Abstract #1840

Relapsed or Refractory Multiple Myeloma Patients Treated with Second-Line Carfilzomib and Categorized by Prior Exposure to Bortezomib: A Subgroup Analysis of the Randomized Phase 3 ASPIRE and ENDEAVOR Trials

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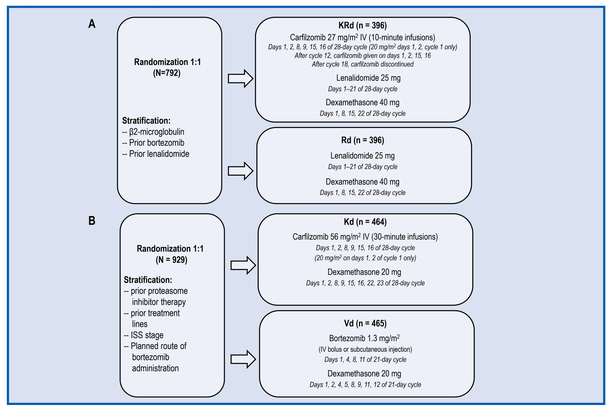
INTRODUCTION

- Carfilzomib is a selective second-generation proteasome inhibitor with a distinct mechanism of action[1] used for the treatment of relapsed or refractory multiple myeloma (RRMM)
- In the randomized phase 3 ASPIRE trial, carfilzomib, lenalidomide, and dexamethasone (KRd) extended progression-free survival (PFS) by 8.7 months (26.3 months vs 17.6 months; hazard ratio [HR]: 0.69; 95% confidence interval [CI]: 0.57–0.83) and overall survival (OS) by 7.9 months (48.3 months vs 40.4 months; HR: 0.79; 95 % CI: 0.67–0.95) compared with lenalidomide and dexamethasone (Rd) in patients with RRMM[2,3]
- In the randomized phase 3 ENDEAVOR trial, carfilzomib and dexamethasone (Kd) extended PFS by 9.3 months (18.7 months vs 9.4 months; HR: 0.53; 95% CI: 0.44–0.65) and OS by 7.6 months (47.6 months vs 40.0 months; HR: 0.79; 95% CI: 0.65–0.96) compared with bortezomib and dexamethasone (Vd) in patients with RRMM[4,5]
- When sequencing therapies in patients with RRMM it is important to understand whether prior exposure to a proteasome inhibitor affects the outcomes of patients who receive carfilzomib
- In this post hoc subgroup analysis of ASPIRE and ENDEAVOR, we studied the efficacy and safety of carfilzomib in subgroups of patients who were previously exposed to bortezomib as a front-line treatment and received second-line carfilzomib

METHODS

- ASPIRE and ENDEAVOR were randomized, open-label, multicenter, phase 3 studies. Patients aged 18 or older who had received one to three prior regimens were eligible
- Data reported here are from preplanned interim analyses of ASPIRE (data cutoff date 16 June 2014) and ENDEAVOR (data cutoff date 10 November 2014)
- In ASPIRE, patients were assigned in a 1:1 ratio to receive either KRd or Rd (Figure 1A), and in ENDEAVOR, patients were assigned 1:1 to receive either Kd or Vd (Figure 1B)
- Patients in ASPIRE and ENDEAVOR received treatment until unacceptable toxicity, progression, or withdrawal of consent. In ASPIRE carfilzomib was discontinued after cycle 18 (after which patients assigned to KRd continued to receive only Rd)
- Disease response was evaluated using the International Myeloma Working Group Uniform Response Criteria.[6] Overall response was defined as achieving a best response of partial response (PR), very good partial response (VGPR), complete response (CR), or stringent complete response (sCR)
- In ASPIRE, prior bortezomib was allowed as long as patients did not progress while receiving bortezomib, and in ENDEAVOR, prior bortezomib was allowed as long as patients had at least a PR to therapy, were not removed from bortezomib therapy due to toxicity, and had at least a 6-month bortezomib treatment-free interval from last dose received until first study treatment
- Patients who received carfilzomib as second-line therapy were assigned to a subgroup:
  (1) Prior bortezomib subgroup (received bortezomib during the first line of therapy)
  (2) Bortezomib-naïve subgroup (did not receive prior bortezomib)
- The *P* values reported for this post hoc analysis are descriptive and were included for exploratory purposes

Figure 1. Design of Randomized Phase 3 Trials. (A) ASPIRE Trial (B) ENDEAVOR Trial



RESULTS

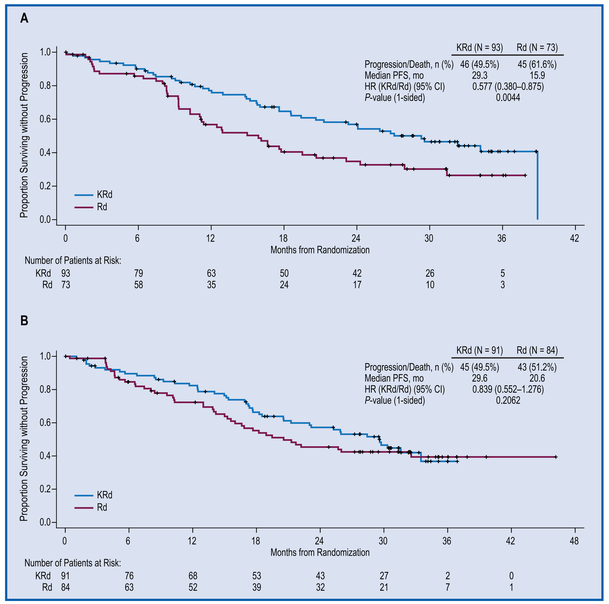
- In ASPIRE, 93/396 patients (23%) in the KRd arm and 73/396 patients (18%) in the Rd arm were included in the prior bortezomib group (treated at first relapse with KRd or Rd)
- In ENDEAVOR, 96/464 patients (21%) in the Kd arm and 101/465 patients (22%) in the Vd arm were included in the prior bortezomib group (treated at first relapse with Kd or Vd)

Table 1. Patient Baseline Demographic and Clinical Characteristics

	ASPIRE				ENDEAVOR			
	Prior Bortezomib		No Prior Bortezomib		Prior Bortezomib		No Prior Bortezomib	
	KRd (n = 93)	Rd (n = 73)	KRd (n = 91)	Rd (n = 84)	Kd (n = 96)	Vd (n = 101)	Kd (n = 136)	Vd (n =131)
Age, median years (range)	64 (40–81)	65 (40–85)	66 (47–87)	68 (41–91)	64 (36–89)	63 (41–85)	67 (38–84)	65 (39–88)
Cytogenetic risk by FISH at study entry, n (%)								
High risk	17 (18.3)	10 (13.7)	6 (6.6)	8 (9.5)	18 (18.8)	26 (25.7)	26 (19.1)	27 (20.6)
Standard risk	29 (31.2)	30 (41.1)	41 (45.1)	42 (50.0)	63 (65.6)	57 (56.4)	86 (63.2)	87 (66.4)
Unknown/missing	47 (50.5)	33 (45.2)	44 (48.4)	34 (40.5)	15 (15.6)	18 (17.8)	24 (17.6)	17 (13.0)
Disease stage at diagnosis, n (%)								
I	18 (19.4)	12 (16.4)	17 (18.7)	17 (20.2)	45 (46.9)	48 (47.5)	64 (47.1)	67 (51.1)
II	22 (23.7)	18 (24.7)	21 (23.1)	19 (22.6)	27 (28.1)	29 (28.7)	41 (30.1)	33 (25.2)
III	46 (49.5)	25 (34.2)	39 (42.9)	37 (44.0)	24 (25.0)	24 (23.8)	31 (22.8)	31 (23.7)
Unknown	7 (7.5)	18 (24.7)	14 (15.4)	11 (13.1)	-	-	-	-

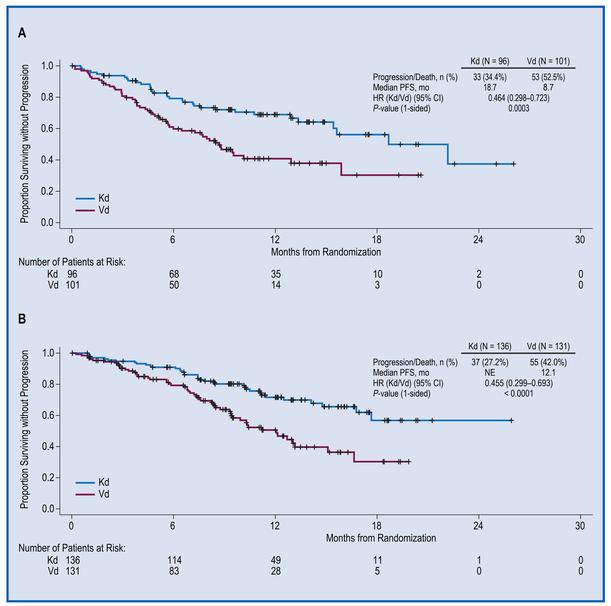
High-risk patients had genetic subtypes t(4; 14), t(14;16), or deletion 17p, while standard-risk patients did not.

Figure 2. Progression-free Survival in the ASPIRE Trial for Patients Treated at First Relapse. (A) Prior Bortezomib (B) No Prior Bortezomib



- In ASPIRE, the median PFS of patients in the prior bortezomib group was 29.3 months (95% CI: 19.4–38.9) for KRd vs 15.9 months (95% CI: 11.1–20.7) for Rd (HR: 0.577; 95% CI: 0.380–0.875; *P* = 0.0044) (Figure 2A)
- The median PFS of patients in the bortezomib-naïve group was 29.6 months (95% CI: 20.6–not evaluable [NE]) for KRd vs 20.6 months (95% CI: 15.6–NE) for Rd (HR: 0.839; 95% CI: 0.552–1.276; *P* = 0.2062) (Figure 2B)

Figure 3. Progression-free Survival in the ENDEAVOR Trial for Patients Treated at First Relapse. (A) Prior Bortezomib (B) No Prior Bortezomib



- In ENDEAVOR, the median PFS of patients in the prior bortezomib group was 18.7 months (95% CI: 15.4–NE) for Kd vs 8.7 months (95% CI: 6.0–12.9) for Vd (HR: 0.464; 95% CI: 0.298–0.723; *P* = 0.0003) (Figure 3A)
- The median PFS of patients in the bortezomib-naïve group was NE (95% CI: 16.8–NE) for Kd vs 12.1 months (95% CI: 9.4–15.1) for Vd (HR: 0.455; 95% CI: 0.299–0.693; *P* < 0.0001) (Figure 3B)

Table 2. Best Overall Response and Overall Response Rate

	ASPIRE				ENDEAVOR			
	Prior Bortezomib		No Prior Bortezomib		Prior Bortezomib		No Prior Bortezomib	
	KRd (n = 93)	Rd (n = 73)	KRd (n = 91)	Rd (n = 84)	Kd (n = 96)	Vd (n = 101)	Kd (n = 136)	Vd (n =131)
Overall response rate, % (95% CI)	86.0 (77.3–92.3)	69.9 (58.0–80.1)	87.9 (79.4–93.8)	70.2 (59.3–79.7)	79.2 (69.7–86.8)	65.3 (55.2–74.5)	83.8 (76.5–89.6)	65.6 (56.9–73.7)
Complete response or better, n (%)	28 (30.1)	5 (6.8)	34 (37.4)	6 (7.1)	9 (9.4)	5 (5.0)	18 (13.2)	13 (9.9)
Very good partial response or better, n (%)	67 (72.0)	33 (45.2)	73 (80.2)	35 (41.7)	52 (54.2)	27 (26.7)	92 (67.6)	44 (33.6)
Best overall response, n (%)								
Stringent complete response	9 (9.7)	3 (4.1)	14 (15.4)	2 (2.4)	2 (2.1)	0 (0)	4 (2.9)	6 (4.6)
Complete response	19 (20.4)	2 (2.7)	20 (22.0)	4 (4.8)	7 (7.3)	5 (5.0)	14 (10.3)	7 (5.3)
Very good partial response	39 (41.9)	28 (38.4)	39 (42.9)	29 (34.5)	43 (44.8)	22 (21.8)	74 (54.4)	31 (23.7)
Partial response	13 (14.0)	18 (24.7)	7 (7.7)	24 (28.6)	24 (25.0)	38 (37.6)	22 (16.2)	42 (32.1)

- In ASPIRE, the ORR (KRd vs Rd) was 86.0% vs 69.9% for patients in the prior bortezomib group and 87.9% vs 70.2% for patients in the bortezomib-naïve group
- In ENDEAVOR, the ORR (Kd vs Vd) was 79.2% vs 65.3% for patients in the prior bortezomib group and 83.8% vs 65.6% for patients in the bortezomib-naïve group

Table 3. Treatment-emergent Adverse Events and Treatment Discontinuation Due to Adverse Events (Safety Population)

	ASPIRE				ENDEAVOR			
	Prior Bortezomib		No Prior Bortezomib		Prior Bortezomib		No Prior Bortezomib	
	KRd (n = 91)	Rd (n = 71)	KRd (n = 91)	Rd (n = 83)	Kd (n = 96)	Vd (n = 98)	Kd (n = 136)	Vd (n = 129)
Any-grade adverse event, n (%)	90 (98.9)	70 (98.6)	88 (96.7)	83 (100.0)	94 (97.9)	97 (99.0)	132 (97.1)	127 (98.4)
Grade ≥ 3 adverse event, n (%)	80 (87.9)	55 (77.5)	76 (83.5)	68 (81.9)	62 (64.6)	56 (57.1)	100 (73.5)	89 (69.0)
Adverse event leading to treatment discontinuation, n (%)	23 (25.3)	18 (25.4)	29 (31.9)	17 (20.5)	14 (14.6)	17 (17.3)	26 (19.1)	25 (19.4)
Fatal adverse event, n (%)	(5.5)	3(4.2)	9 (9.9)	7 (8.4)	5 (5.2)	3 (3.1)	5 (3.7)	4 (3.1)

- In ASPIRE, rates of grade ≥ 3 adverse events (KRd vs Rd) for patients in the prior bortezomib group were 87.9% vs 77.5% and for bortezomib-naïve patients were 83.5% vs 81.9%
- In ENDEAVOR, rates of grade ≥ 3 adverse events (Kd vs Vd) for patients in the prior bortezomib group were 64.6% vs 57.1% and for bortezomib-naïve patients were 73.5% vs 69.0%

CONCLUSIONS

- Carfilzomib-based regimens were effective at first relapse compared to standard of care, regardless of prior exposure to bortezomib
- In ASPIRE, KRd improved PFS compared to Rd at first relapse after bortezomib-based frontline therapy, providing 13.4 additional months without disease progression (29.3 months vs 15.9 months)
- In ENDEAVOR, Kd improved PFS compared to Vd at first relapse after bortezomib-based frontline therapy, providing 10.0 additional months without disease progression (18.7 months vs 8.7 months)
- Safety results for the prior bortezomib and no prior bortezomib subgroups were comparable to those previously reported for the ASPIRE and ENDEAVOR trials[2,4]
- These findings demonstrate that proteasome inhibitor–sensitive patients can benefit from carfilzomib therapy at first relapse after prior bortezomib treatment

ACKNOWLEDGMENTS

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DISCLOSURES

MVM has received honoraria from Janssen, Celgene, Amgen, and Takeda. HG has received consulting fees from Amgen, Bristol-Myers Squibb, Celgene, Janssen, Novartis, and Takeda; honoraria from Bristol-Myers Squibb, Celgene, Chugai, Janssen, and Novartis; and research funding from Bristol-Myers Squibb, Celgene, Chugai, Janssen, and Novartis. JS-M has received consulting fees from Bristol-Myers Squibb, Celgene, Janssen, Millennium, Merck Sharp & Dohme, Novartis, Sanofi, Roche, and Amgen. JM reports that AbbVie, Celgene, and Sanofi have contracted research with Mayo Clinic. LZ is an employee of and owns stock in Amgen. MO is an employee of and owns stock in Amgen. JB is an employee of and owns stock in Amgen. KI is an employee of and owns stock in Amgen. XL has received honoraria and consulting fees from and is on advisory committees for Janssen, Celgene, BMS, Takeda, Amgen, Merck, Novartis, Pierre Fabre, Abbvie, Sanofi, Gilead, and Roche.

Abstract #1840

Overall Survival of Patients With Relapsed Multiple Myeloma Treated With Carfilzomib and Dexamethasone Versus Bortezomib and Dexamethasone According to Prior Line of Therapy and Previous Exposure to Bortezomib: Secondary Analysis of the Phase 3 ENDEAVOR Study

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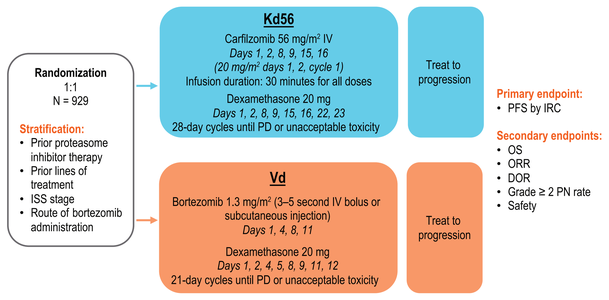
INTRODUCTION

- The phase 3 ENDEAVOR study showed a significant improvement in progression-free survival (PFS) for carfilzomib at the 56 mg/m^2 dose combined with dexamethasone (Kd56) vs bortezomib and dexamethasone (Vd) in patients with relapsed and/or refractory multiple myeloma (RRMM)[1]
  - The PFS benefit with Kd56 vs Vd was seen regardless of the number of lines of prior therapy and prior exposure to bortezomib[2]
- In the overall survival (OS) analysis of ENDEAVOR, median OS was significantly improved by almost 8 months for patients who received Kd56 than for patients who received Vd (47.6 vs 40.0 months; hazard ratio [HR] for Kd56 vs Vd = 0.79; 95% confidence interval [CI]: 0.65, 0.96; 1-sided P = 0.0100)[3]
- Here, we present OS and safety analyses comparing Kd56 with Vd according to prior lines of therapy and previous exposure to bortezomib

METHODS

Figure 1. ENDEAVOR Study Design



DOR, duration of response; IRC, independent review committee; ISS, International Staging System; IV, intravenous; Kd56, carfilzomib and dexamethasone; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PN, peripheral neuropathy; Vd, bortezomib and dexamethasone

Figure 2. ENDEAVOR Key Eligibility Criteria

Inclusion:
- Adults ≥ 18 years with RRMM
- 1-3 prior treatments
- ECOG PS 0–2
- PR or better to at least 1 prior regimen
- Prior treatment with bortezomib or carfilzomib allowed if:
  - ≥ PR to prior treatment
  - ≥ 6 months free of PI treatment
  - Treatment was not stopped due to toxicity

Exclusion:
- Grade 3 or 4 PN within 14 days prior to randomization
- Myocardial infarction within 4 months prior to randomization
- New York Heart Association class III or IV heart failure
- LVEF < 40%
- Creatinine clearance < 15 mL/min

ECOG PS, Eastern Cooperative Oncology Group performance status; LVEF, left ventricular ejection fraction; PI, proteasome inhibitor; PN, peripheral neuropathy; PR, partial response; RRMM, relapsed and/or refractory multiple myeloma

Statistics

- An unstratified log-rank test was used to compare OS between treatment arms for each prespecified subgroup
- The Kaplan-Meier OS rate and median OS were estimated up to the time point when there were 10 or fewer patients (Kd56 and Vd combined) in the risk set
- The study was not powered to detect differences in OS between prespecified subgroups.
- Adverse events (AEs) are presented as preferred terms, not adjusted for exposure

RESULTS

Enrollment and patient demographics

- A total of 929 patients were randomized to receive Kd56 (n = 464) or Vd (n = 465)
- Patient demographics were generally balanced between the Kd56 and Vd treatment arms by prior lines of therapy, and prior and no prior bortezomib treatment (Table 1) except:
  - There was an imbalance in prior thalidomide exposure in the subgroups, which was greatest between Kd56 and Vd in the 1 prior line subgroup
  - A lower proportion of patients in the Kd56 arm vs the Vd arm had International Staging System stage 2–3 disease in the 2–3 prior-lines subgroup

Table 1. Patient and Disease Characteristics at Baseline

	1 prior line		2–3 prior lines		No Prior Bortezomib		Prior Bortezomib	
Characteristic	Kd56 (n = 231)	Vd (n = 229)	Kd56 (n = 233)	Rd (n = 236)	Kd56 (n = 214)	Vd (n = 213)	Kd56 (n = 250)	Vd (n = 252)
Age, years, median (range)	66.0 (36, 89)	63.0 (39, 88)	64.0 (35, 89)	66.5 (30, 86)	66.0 (35, 84)	66.0 (30, 88)	64.0 (36, 89)	65.0 (41, 85)
Age ≥ 75, years, %	19.0	11.4	14.2	16.9	16.8	17.4	16.4	11.5
ISS stage, %								
1	46.8	50.7	44.6	37.7	45.8	47.4	45.6	41.3
2–3	53.2	49.3	55.4	62.3	54.2	52.6	54.4	58.7
Cytogenetic risk by FISH,[a] %								
High	22.0	27.3	28.9	28.6	24.3	28.1	26.5	27.9
Standard	78.0	72.7	71.1	71.4	75.7	71.9	73.5	72.1
Prior therapies, %								
Bortezomib	42.0	42.8	65.7	65.3	—	—	100	100
Carfilzomib	0.4	0	0.4	0.4	0.9	0.5	—	—
Lenalidomide	22.1	20.1	54.1	55.9	35.5	39.0	40.4	37.7
Thalidomide	38.1	49.8	53.2	57.2	57.0	65.3	36.0	43.7
Number of prior regimens, %								
1	99.1	99.6	1.3	1.3	63.6	61.5	38.4	39.7
2	0.9	0.4	67.0	60.6	24.8	27.2	42.0	34.1
3	—	—	37.3	31.8	11.7	10.8	19.6	25.8
4	—	—	0	0.8	0	0.5	0	0.4
Bortezomib refractory, %	0	0	6.4	6.8	0	0	6.0	6.3

[a]Percentages are calculated as a proportion of the number of patients with known cytogenetics.
FISH, fluorescent in situ hybridization; ISS, International Staging System; Kd56, carfilzomib at the 56 mg/m^2 dose combined with dexamethasone; Vd, bortezomib and dexamethasone.

ENDEAVOR OS Analysis

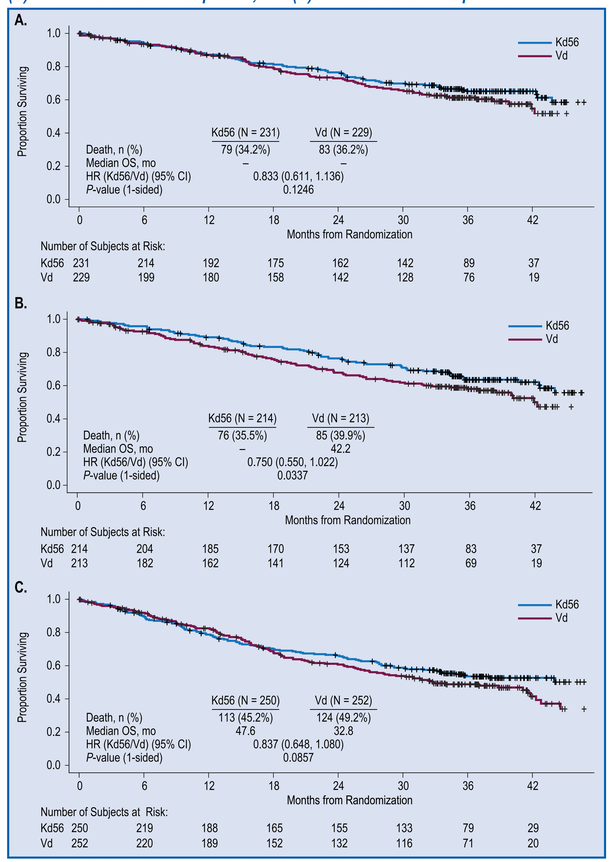
- The OS analysis was done when 79% of the targeted survival events occurred. At the data cutoff date of 3-Jan-2017, with a median OS follow-up of approximately 37 months, the OS met statistical significance
- In the ITT population, the OS rate at 24 months (Kd56 vs Vd) was 70.9% vs 63.9%. At 24 months, in the ITT population, Kd56 treatment reduced the risk of death by 21% (HR = 0.79; 95% CI, 0.62, 0.99) compared to Vd
- The risk of death was low in patients at first relapse, and it was not possible to reliably estimate median OS for the Kd56 and Vd arms in the 1 prior line subgroup (Table 2 and Figure 3A)
  - The HR of 0.83 (95% CI: 0.61, 1.14) suggested a survival advantage for Kd56 vs Vd in patients at first relapse
- Kd56 improved survival by 11.8 months vs Vd (median OS for Kd56 vs Vd, 40.5 vs 28.7 months; HR = 0.76; 95% CI: 0.59, 0.99) for patients with 2–3 prior lines of therapy (Table 2)
- For patients without prior bortezomib exposure, the median OS was not reached in the Kd56 arm and was 42.2 months in the Vd arm (HR = 0.75; 95% CI: 0.55, 1.02) (Table 2 and Figure 3B)
- Kd56 improved survival by 14.8 months compared with Vd (median OS for Kd56 vs Vd, 47.6 months vs 32.8 months; HR = 0.84; 95% CI: 0.65, 1.08) for patients with prior bortezomib exposure (Table 2 and Figure 3C)

Table 2. Survival Outcome According to Prior Line of Therapy and Prior Bortezomib Exposure

	1 prior line		2–3 prior lines		No Prior Bortezomib		Prior Bortezomib	
Outcome	Kd56 (n = 231)	Vd (n = 229)	Kd56 (n = 233)	Rd (n = 236)	Kd56 (n = 214)	Vd (n = 213)	Kd56 (n = 250)	Vd (n = 252)
Median OS, months, (95% CI)	–	–	40.5 (31.7, –)	28.7 (22.9, 40.0)	–	42.2 (36.8, –)	47.6 (33.6, –)	32.8 (26.5, 41.8)
OS HR for Kd56 vs Vd (95% CI)	0.83 (0.61, 1.14) P = 0.125		0.76 (0.59, 0.99) P = 0.020		0.75 (0.55, 1.02) P = 0.034		0.84 (0.65, 1.08) P = 0.086	
Median follow-up time for OS,[a] months, (95% CI)	37.5 (36.3, 38.6)	36.6 (35.4, 37.5)	37.5 (36.5, 38.8)	37.3 (36.2, 38.4)	37.7 (36.3, 38.7)	36.9 (35.6, 38.0)	37.3 (36.5, 38.5)	36.9 (35.5, 37.7)
Median PFS,[b,c] months	22.2	10.1	14.9	8.4	–	11.2	15.6	8.1
PFS HR for Kd56 vs Vdb,[c] (95% CI), P-value	0.45 (0.33, 0.61) P < 0.0001		0.60 (0.47, 0.78) P < 0.0001		0.48 (0.35, 0.66) P < 0.0001		0.56 (0.44, 0.73) P < 0.0001	

"–", not estimable.
[a]Median follow-up times were estimated using the reverse Kaplan-Meier method (Schemper and Smith, 1996). Corresponding 95% CIs were estimated using the method by Klein and Moeschberger (1997) with log-log transformation.
[b]PFS outcomes by prior lines of therapy and prior bortezomib treatment (Moreau et al. *Leukemia*. 2017;31:115-122).
[c]Kd56- and Vd-treated patients evaluated for PFS in treatment subgroups: 1 prior line, 232 (Kd56) and 232 (Vd); 2–3 prior lines, 232 (Kd56) and 233 (Vd); no prior bortezomib, 214 (Kd56) and 213 (Vd); prior bortezomib, 250 (Kd56) and 252 (Vd).
CI, confidence interval; HR, hazard ratio; Kd56, carfilzomib and dexamethasone; OS, overall survival; PFS, progression-free survival; Vd, bortezomib and dexamethasone.

Figure 3. Kaplan-Meier OS Curves by Prior Treatment: (A) 1 Prior Line of Therapy, (B) No Prior Bortezomib Exposure, and (C) Prior Bortezomib Exposure



For the subgroup of patients with 1 prior line (A), no prior bortezomib (B), and prior bortezomib subgroups (C), curves were displayed to the time point when there were 10 patients or fewer (Kd56 and Vd combined) at risk (Pocock et al. *Lancet*. 2002;359:1686-1689)
"–"denotes not estimable.
CI, confidence interval; HR, hazard ratio; Kd56, carfilzomib at the 56 mg/m^2 dose combined with dexamethasone; OS, overall survival; Vd, bortezomib and dexamethasone

AEs

- The frequency of grade ≥ 3 AEs was 78.4% (Kd56) and 68.3% (Vd) in the 1 prior line subgroup, and 84.5% (Kd56) and 73.7% (Vd) in the 2–3 prior line subgroup (Table 3)
- Grade ≥ 3 AEs were reported in 83.2% (Kd56) and 77.3% (Vd) of patients with no prior bortezomib exposure, and 79.9% (Kd56) and 65.7% (Vd) of patients with prior bortezomib exposure (Table 3)
  - The frequency of grade ≥ 3 anemia, hypertension, cardiac failure, and dyspnea was higher for Kd56 vs Vd in all subgroup
  - The incidence of Grade ≥ 3 diarrhea and peripheral neuropathy was lower for Kd56 than Vd in all subgroups
  - The incidence of grade ≥ 3 acute renal failure was numerically higher for Kd56 vs Vd in the 2–3 prior line and prior bortezomib subgroups, but lower for Kd vs Vd in 1 prior line and bortezomib naïve subgroups
- Rates of AEs leading to treatment discontinuation and death (grade 5 AEs) were similar between the Kd56 and Vd treatment arms for all subgroups

Table 3. Summary of Adverse Events (AEs)

	1 prior line		2–3 prior lines		No Prior Bortezomib		Prior Bortezomib	
Characteristic	Kd56 (n = 231)	Vd (n = 229)	Kd56 (n = 233)	Rd (n = 236)	Kd56 (n = 214)	Vd (n = 213)	Kd56 (n = 250)	Vd (n = 252)
Treatment duration, weeks, median (range)	52 (1, 213)	28 (1, 198)	42 (1, 211)	25 (1, 198)	54 (1, 211)	26 (1, 198)	44 (1, 213)	27 (1, 178)
Grade ≥ 3 AEs, %	78.4	68.3	84.5	73.7	83.2	77.3	79.9	65.7
Grade ≥3 hematologic AEs, %								
Anemia	15.2	8.5	17.7	11.6	14.0	11.4	18.5	9.0
Thrombocytopenia	6.5	8.5	11.2	10.3	6.5	10.9	10.8	8.2
Neutropenia	0.9	1.8	3.9	2.6	1.4	1.9	3.2	2.4
Grade ≥3 nonhematolgic AEs, %								
Pneumonia	8.7	7.1	9.5	9.9	7.9	9.0	10.0	8.2
Fatigue	7.4	8.5	6.0	6.9	9.3	9.5	4.4	6.1
Diarrhea	2.2	5.8	5.6	11.2	3.7	10.9	4.0	6.5
Grade ≥3 AEs of interest, %								
Hypertension	15.2	4.0	13.8	2.6	19.2	5.2	10.4	1.6
Cardiac failure	3.0	0.4	2.6	0.9	3.3	0.5	2.4	0.8
Dyspnea	5.6	2.2	6.9	2.2	5.1	1.9	7.2	2.4
PN	2.2	6.3	0.4	6.0	1.9	8.5	0.8	4.1
Acute renal failure	1.3	2.2	3.9	0.9	2.3	2.8	2.8	0.4
AEs leading to treatment discontinuation, %	25.1	20.5	25.0	22.8	26.6	23.7	23.7	20.0
Grade 5 AEs, %	6.5	3.1	7.3	6.0	4.7	4.3	8.8	4.9

AEs were coded using Medical Dictionary for Regulatory Activities version 15.1, and patients were counted once for each preferred term; AEs were not adjusted for exposure.
AE, adverse event; Kd56, carfilzomib at the 56 mg/m^2 dose combined with dexamethasone; PN, peripheral neuropathy; Vd, bortezomib and dexamethasone.

CONCLUSIONS

- Treatment with Kd56 showed a survival benefit compared with Vd in patients with RRMM regardless of the number of prior lines of therapy and previous exposure to bortezomib
  - Kd56 extended PFS by 12.1 months and 6.5 months in patients at first relapse and in patients with 2–3 prior lines of therapy, respectively, and reduced the risk of death by 17% (1 prior line) and 24% (2–3 prior lines)
  - Kd56 prolonged PFS by 7.5 months and OS by 14.8 months vs retreatment with bortezomib in proteasome inhibitor–sensitive patients.
- In general, treatment was well tolerated; the rate of AEs in this subgroup analysis was consistent with that reported in the overall ENDEAVOR population

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Overall Survival of Relapsed/Refractory Multiple Myeloma Patients Treated With Carfilzomib and Dexamethasone vs Bortezomib and Dexamethasone: Results from the Phase 3 ENDEAVOR Study According to Age Subgroup

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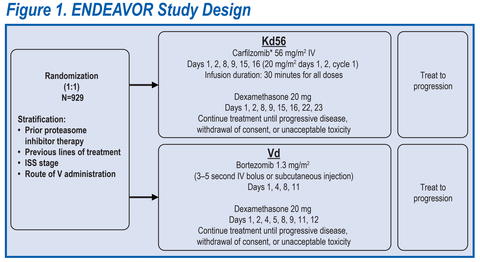
INTRODUCTION

- Elderly patients with multiple myeloma can be challenging to treat, as aging is associated with a greater burden of comorbidities and frailty, and elderly patients may experience increased toxicity from cancer drugs[1,2]
- Carfilzomib, a selective proteasome inhibitor, is approved in the United States and Europe for the treatment of relapsed or refractory multiple myeloma (RRMM) in combination with lenalidomide plus dexamethasone or with dexamethasone alone[3]
- The phase 3 ENDEAVOR study was the first clinical trial comparing carfilzomib with bortezomib, a first-generation proteasome inhibitor; the primary endpoint of ENDEAVOR was progression-free survival (PFS)[4]
- A subgroup analysis of interim results from ENDEAVOR showed that carfilzomib (56 mg/m^2) and dexamethasone (Kd56) resulted in longer median PFS and higher overall response rates (ORRs) than bortezomib and dexamethasone (Vd) in patients with RRMM, regardless of age[5]
- Mature overall survival (OS) data from ENDEAVOR has demonstrated that Kd56 resulted in statistically and clinically significant improvement in OS compared with Vd in the intent-to-treat (ITT) population (median, 47.6 months vs 40.0 months; hazard ratio [HR], 0.791; 95% confidence interval [CI], 0.648–0.964; 1-sided P=0.0100)[6]
- Here, we report a subgroup analysis from ENDEAVOR to evaluate OS and updated safety outcomes by age

METHODS

- ENDEAVOR was a phase 3, randomized, open-label, multicenter study. Adults with RRMM who received 1–3 prior regimens were eligible
  - Patients with active congestive heart failure (New York Heart Association Class III to IV), symptomatic ischemia, conduction abnormalities uncontrolled by conventional intervention, or myocardial infarction within 4 months prior to randomization were excluded
- Patients were randomized 1:1 to receive Kd56 or Vd, and treatment was given until disease progression, withdrawal of consent, or unacceptable toxicity **(Figure 1)**
- Disease response and progression were evaluated using the International Myeloma Working Group Uniform Response Criteria.[7] Overall response was defined as achieving a best overall response of partial response, very good partial response, complete response, or stringent complete response
- In this post-hoc subgroup analysis, OS was compared between treatment arms in patients grouped according to age (i.e., <65, 65–74, and ≥75 years of age) using an unstratified Cox proportional hazards model
- Adverse events were not adjusted for exposure

Figure 1. ENDEAVOR Study Design



*Carfilzomib was administered for 3 weeks out of 4.
ISS, International Staging System; IV, intravenous; Kd56, carfilzomib and dexamethasone; PD, progression disease; V, bortezomib; Vd, bortezomib and dexamethasone.

RESULTS

- The ITT population included 929 patients enrolled at sites in North and South America, Eastern and Western Europe, and Asia-Pacific:
  - <65 years: Kd56, n=223; Vd, n=210
  - 65–74 years: Kd56, n=164; Vd, n=189
  - ≥75 years: Kd56, n=77; Vd, n=66
- Baseline and demographic characteristics were generally balanced between treatment arms within the 3 age subgroups **(Table 1)**[5]

Table 1. Patient Demographics and Baseline Disease Characteristics[5]

	<65 years		65–74 years		≥75 years	
	Kd56 (n=223)	Vd (n=210)	Kd56 (n=164)	Vd (n=189)	Kd56 (n=77)	Vd (n=66)
Age, median years (range)	58.0 (35.0–64.0)	59.0 (30.0–64.0)	69.0 (65.0–74.0)	69.0 (65.0–74.0)	78.0 (75.0–89.0)	77.5 (75.0–88.0)
ECOG PS, n (%)						
0	119 (53.4)	111 (52.9)	71 (43.3)	93 (49.2)	31 (40.3)	28 (42.4)
1	95 (42.6)	81 (38.6)	80 (48.8)	88 (46.6)	36 (46.8)	34 (51.5)
2	9 (4.0)	18 (8.6)	13 (7.9)	8 (4.2)	10 (13.0)	4 (6.1)
Cytogenetic risk by FISH at study entry, n (%)[a,b]						
High risk	48 (26.1)	52 (28.3)	33 (24.3)	49 (29.7)	16 (26.2)	12 (21.8)
Standard risk	136 (73.9)	132 (71.7)	103 (75.7)	116 (70.3)	45 (73.8)	43 (78.2)
Creatinine clearance, n (%)						
≥15 to <50 mL/min	22 (9.9)	22 (10.5)	28 (17.1)	44 (23.3)	35 (45.5)	33 (50.0)
50 to <80 mL/min	64 (28.7)	53 (25.2)	85 (51.8)	97 (51.3)	37 (48.1)	27 (40.9)
≥80 mL/min	137 (61.4)	135 (64.3)	51 (31.1)	48 (25.4)	5 (6.5)	6 (9.1)
ISS stage at baseline, n (%)						
Stage 1	121 (54.3)	109 (51.9)	70 (42.7)	80 (42.3)	21 (27.3)	16 (24.2)
Stage 2	53 (23.8)	64 (30.5)	56 (34.1)	62 (32.8)	29 (37.7)	25 (37.9)
Stage 3	49 (22.0)	37 (17.6)	38 (23.2)	47 (24.9)	27 (35.1)	25 (37.9)
Prior therapy, n (%)						
Bortezomib	134 (60.1)	116 (55.2)	75 (45.7)	107 (56.6)	41 (53.2)	29 (43.9)
Lenalidomide	78 (35.0)	58 (27.6)	69 (42.1)	88 (46.6)	30 (39.0)	31 (47.0)
Number of prior regimens[c]						
1	102 (45.7)	125 (59.5)	86 (52.4)	80 (42.3)	44 (57.1)	27 (40.9)
2	91 (40.8)	56 (26.7)	43 (26.2)	62 (32.8)	23 (29.9)	27 (40.9)
3	30 (13.5)	28 (13.3)	35 (21.3)	47 (24.9)	10 (13.0)	12 (18.2)

[a]The high-risk group consisted of patients with the genetic subtype t(4;14) or t(14;16) in ≥10% of screened plasma cells or with del(17p) in ≥20% of screened plasma cells. The standard-risk group consisted of all other patients with available and known baseline cytogenetics. The unknown/missing cytogenetics subgroup included patients who had a FISH assessment, but were either not analyzable or did not yield a definitive result.
[b]Percentage is based on the number of patients with known cytogenetic risk status.The number of patients (percentage out of total patients in each group) with unknown/missing cytogenetic risk status is as follows: <65 years, Kd56=39 (17.5) and Vd=26 (12.4); 65–74 years, Kd56=28 (17.1) and Vd=24 (12.7); ≥75 years, Kd56=16 (20.8) and Vd=11 (16.7).
[c]One patient (age <65 years; Vd) had 4 prior regimens.
ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in-situ hybridization; ISS, International Staging System; Kd56, carfilzomib and dexamethasone; Vd, bortezomib and dexamethasone.

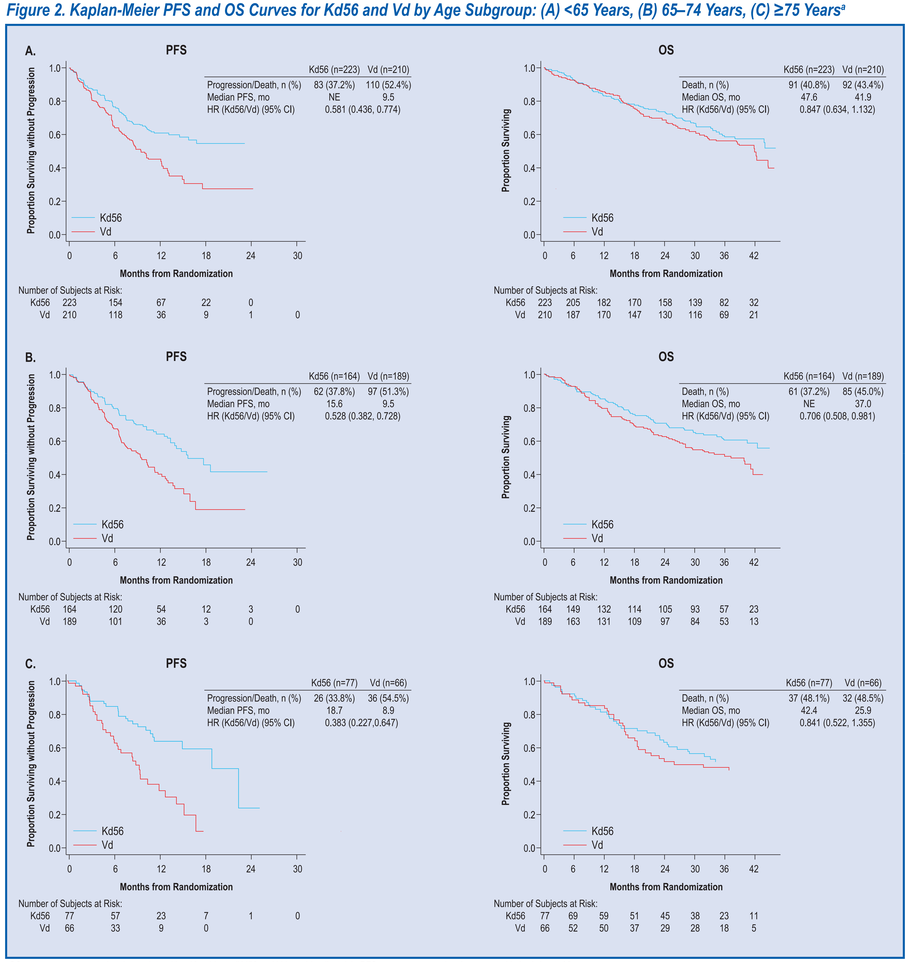
- OS was improved for patients treated with Kd56 vs Vd in all 3 age subgroups (median OS: <65 years, 47.6 months vs 41.9 months [HR (95% CI), 0.847 (0.634–1.132)]; 65–74 years, not reached vs 37.0 months [HR (95% CI), 0.706 (0.508–0.981)]; ≥75 years, 42.4 months vs 25.9 months [HR (95% CI), 0.841 (0.522–1.355)]; **Table 2, Figure 2**)
- Both the ORR and the rate of achieving complete response or better were higher for Kd56 vs Vd across all age subgroups **(Table 2)**

Table 2. Efficacy Outcomes by Age Subgroup

	<65 years		65–74 years		≥75 years	
	Kd56 (n=223)	Vd (n=210)	Kd56 (n=164)	Vd (n=189)	Kd56 (n=77)	Vd (n=66)
Median OS, months	47.6	41.9	Not reached	37.0	42.4	25.9
HR for Kd56 vs Vd (95% CI)	0.847 (0.634–1.132)		0.706 (0.508–0.981)		0.841 (0.522–1.355)	
Median PFS, months[a]	Not reached	9.5	15.6	9.5	18.7	8.9
HR for Kd56 vs Vd (95% CI)	0.581 (0.436–0.774)		0.528 (0.382–0.728)		0.383 (0.227–0.647)	
Best overall response, n (%)						
CR+	35 (15.7)	16 (7.6)	19 (11.6)	11 (5.8)	4 (5.2)	2 (3.0)
VGPR+	118 (52.9)	64 (30.5)	88 (53.7)	54 (28.6)	46 (59.7)	15 (22.7)
Overall response rate, % (95% CI)	74.0 (67.7–79.6)	61.0 (54.0–67.6)	77.4 (70.3–83.6)	65.6 (58.4–72.4)	84.4 (74.4–91.7)	59.1 (46.3–71.0)

[a]PFS and best overall response data are from the PFS interim analysis data cut.[5]
CI, confidence interval; CR+, complete response or better; HR, hazard ratio; Kd56, carfilzomib and dexamethasone; NE, not estimable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR+, partial response or better; Vd, bortezomib and dexamethasone; VGPR+, very good partial response or better.

Figure 2. Kaplan-Meier PFS and OS Curves for Kd56 and Vd by Age Subgroup: (A) <65 Years, (B) 65–74 Years, (C) ≥75 Years[a]



[a]OS curves were truncated at time points with ≤10 subjects (Kd56 and Vd combined) at risk. PFS curves were previously presented in Ludwig et al.[5]
CI, confidence interval; HR, hazard ratio; Kd56, carfilzomib and dexamethasone; NE, not estimable; OS, overall survival; PFS, progression-free survival; Vd, bortezomib and dexamethasone.

- In the safety population (n=919), the median duration of treatment was longer with Kd56 than with Vd within each age subgroup (<65 years: median, 49.0 weeks vs 27.0 weeks; 65–74 years: 49.9 weeks vs 27.6 weeks; ≥75 years: 43.3 weeks vs 20.6 weeks)
- The incidence of grade ≥3 peripheral neuropathy was lower for Kd56 than Vd across all age subgroups **(Table 3)**
- The incidence of grade ≥3 hypertension, dyspnea, cardiac failure, acute renal failure, and cardiac ischemia were greater with Kd56 vs Vd across all age subgroups **(Table 3)**
  - Treatment discontinuation due to hypertension was rare, with only one patient in the Kd arm stopping treatment
- Grade 5 AEs that occurred in ≥2 patients in a subgroup were pneumonia (<65 years: Kd56, n=1; Vd, n=1; 65–74 years: no events; ≥75 years: Kd56, n=2; Vd, n=1), septic shock (<65 years: Kd56, n=0; Vd, n=1; 65–74 years: Kd56, n=2; Vd, n=1; ≥75 years: Kd56, n=1; Vd, n=0), sudden death (<65 years: Kd56, n=1; Vd, n=0; 65–74 years: Kd56, n=0; Vd, n=1; ≥75 years: Kd56, n=2; Vd, n=0), and cardiac arrest (<65 years: no events; 65–74 years: Kd56, n=2; Vd, n=0; ≥75 years: Kd56, n=0; Vd, n=1)

Table 3. Incidence of Adverse Events by Age Subgroup[a]

	<65 years		65–74 years		≥75 years	
	Kd56 (n=223)	Vd (n=208)	Kd56 (n=163)	Vd (n=183)	Kd56 (n=77)	Vd (n=65)
Treatment-emergent AEs, n (%)	220 (98.7)	207 (99.5)	160 (98.2)	180 (98.4)	77 (100.0)	64 (98.5)
Grade ≥3 hematologic related AEs, n (%)						
Anemia	36 (16.1)	23 (11.1)	22 (13.5)	20 (10.9)	18 (23.4)	3 (4.6)
Thrombocytopenia	17 (7.6)	19 (9.1)	17 (10.4)	19 (10.4)	7 (9.1)	5 (7.7)
Neutropenia	7 (3.1)	4 (1.9)	4 (2.5)	5 (2.7)	0	1 (1.5)
Leukopenia	2 (0.9)	1 (0.5)	3 (1.8)	1 (0.5)	0	0
Grade ≥3 AEs of interest,[b] n (%)						
Hypertension	31 (13.9)	7 (3.4)	23 (14.1)	6 (3.3)	13 (16.9)	2 (3.1)
Peripheral neuropathy	2 (0.9)	7 (3.4)	4 (2.5)	17 (9.3)	0	4 (6.2)
Dyspnea	9 (4.0)	3 (1.4)	14 (8.6)	6 (3.3)	6 (7.8)	1 (1.5)
Acute renal failure	8 (3.6)	6 (2.9)	1 (0.6)	1 (0.5)	3 (3.9)	0
Cardiac failure	3 (1.3)	1 (0.5)	6 (3.7)	1 (0.5)	4 (5.2)	1 (1.5)

[a]Incidence of adverse events was not adjusted for exposure.
[b]Preferred term.
AE, adverse event; Kd56, carfilzomib and dexamethasone; Vd, bortezomib and dexamethasone.

CONCLUSIONS

- **Clinically meaningful improvements in OS were observed with Kd56 compared with Vd across all age groups examined, including in elderly patients (aged ≥75 years)**
  - **<65 years, 5.7-month improvement in median OS; HR (95% CI), 0.847 (0.634–1.132)**
  - **65–74 years, improvement in median OS not estimable; HR (95% CI), 0.706 (0.508–0.981)**
  - **≥75 years, 16.5-month improvement in median OS; HR (95% CI), 0.841 (0.522–1.355). This gain of more than 1 year for OS occurred despite a higher proportion of these patients having advanced disease stage and reduced renal function**
- **Safety results were comparable to those reported in the age subgroup analysis of the PFS interim results for ENDEAVOR[5]**
- **Overall, these data support the favorable benefit-risk profile of Kd56 in patients with RRMM, regardless of age**

CONFLICT OF INTEREST DISCLOSURE

RN received personal fees from Celgene and Millennium. **HL** received research funding from Takeda and Amgen; served as a consultant and on the speakers' bureau for Takeda, Amgen, and Cllag-Janssen; and served on the speakers' bureau for Celgene and BMS. **AS** received research funding and honoraria from, and served as a consultant for, Amgen. **HG** received research support from Celgene, Janssen, Chugai, Novartis, BMS; attended advisory boards and served as consultant for Janssen, Celgene, Novartis, Amgen, Takeda, BMS; and received honoraria from Celgene, Janssen, Novartis, Chugai, and BMS. **TP** has no disclosures to report. **MVM** received honoraria from, and served as a consultant for, Celgene and Takeda. **MD** served as a consultant for Amgen, Celgene, Janssen, Novartis, and Takeda. **LZ** and **ASK** are employees and equity owners of Amgen, Inc. **TF** served on the speakers' bureau for Amgen and Celgene.

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Rates of Peripheral Neuropathy in Patients with Relapsed and Refractory Multiple Myeloma Treated with Carfilzomib vs Comparators in Pivotal Phase 3 Trials

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INTRODUCTION

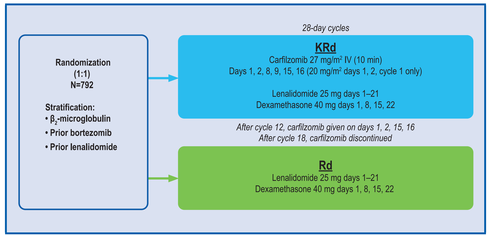
- Peripheral neuropathy (PN) is a common complication of multiple myeloma (MM) or its treatment, and it can cause severe symptoms (including pain) and impair quality of life[1]
- PN is a dose-limiting toxicity for the proteasome inhibitor bortezomib
  - One meta-analysis found an increased risk of grade 3 or 4 PN among patients with MM who were treated with bortezomib compared with those who were not (13.8% vs 4.4%, respectively)[2]
  - PN is among the most common adverse events leading to treatment discontinuation of bortezomib[2–5]
- There is a need for new anti-MM regimens with improved PN tolerability profiles to allow for more effective and sustained anti-MM therapy
- Carfilzomib is an irreversible proteasome inhibitor that has been approved worldwide in patients with relapsed or refractory multiple myeloma (RRMM) either as a single agent or in combination with dexamethasone or lenalidomide and dexamethasone
  - In phase 2 studies, single-agent carfilzomib has been associated with low rates of PN
- The approvals of carfilzomib (27 mg/m^2), lenalidomide, and dexamethasone (KRd) and carfilzomib (56 mg/m^2) and dexamethasone (Kd56) were based on interim results from 2 randomized, phase 3 trials of RRMM patients (1–3 prior lines of therapy): ASPIRE and ENDEAVOR
  - ASPIRE (NCT01080391): KRd resulted in superior progression-free survival (PFS) vs lenalidomide plus dexamethasone (Rd) (median 26.3 vs 17.6 months, respectively; hazard ratio [HR], 0.69; 95% confidence interval [CI], 0.57–0.83; *P*=0.0001)[6]
  - ENDEAVOR (NCT01568866): Kd56 resulted in superior PFS vs bortezomib plus dexamethasone (Vd) (median 18.7 vs 9.4 months, respectively; HR, 0.53; 95% CI, 0.44–0.65; *P*<0.0001)[7]
    - In a second interim overall survival (OS) analysis of ENDEAVOR, Kd56 provided a statistically significant 21% reduction in the risk of death and a 7.6-month improvement in median OS compared with Vd[8]
- This analysis evaluated PN rates, patient-reported outcomes (PROs) related to PN, and PFS by baseline history of PN in ASPIRE and ENDEAVOR

METHODS

ASPIRE Study

- The study design for ASPIRE is shown in **Figure 1**
  - Patients with significant neuropathy (grades 3–4, or grade 2 with pain) within 14 days prior to randomization were excluded
- Data on adverse events, including PN, were collected until 30 days after administration of the last dose of study treatment, and events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0
- The pain subscale of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30) was a prespecified exploratory end point (assessed in the intention-to-treat [ITT] population)
  - The pain subscale is scored from 0–100, with higher scores indicating more severe symptoms
  - Pain subscale scores were compared between treatment groups using a restricted maximum likelihood–based mixed model for repeated measures under the assumption of missing at random

Figure 1. ASPIRE Study Design

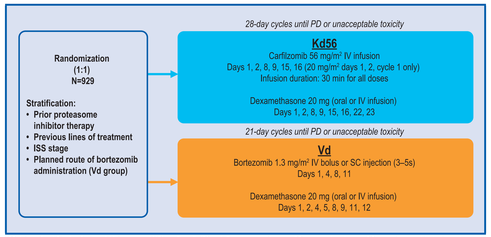


IV, intravenous; KRd, carfilzomib, lenalidomide, and dexamethasone; Rd, lenalidomide and dexamethasone.

ENDEAVOR Study

- The study design for ENDEAVOR is shown in **Figure 2**
  - Patients with significant neuropathy (grades 3–4, or grade 2 with pain) within 14 days prior to randomization were excluded
- Adverse event data, including PN, were collected until 30 days after last dose of study treatment. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.
- The incidence of grade ≥2 PN events (Standardized MedDRA query, narrow scope [SMQN]) was a prespecified key secondary end point
- The QLQ-C30 pain subscale and the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity subscale (FACT/GOG-NTx) were prespecified exploratory end points
  - The pain subscale was assessed in the ITT population; the NTx subscale was assessed in the safety population
  - The pain subscale is scored from 0–100 with higher scores indicating more severe symptoms; the NTx subscale is scored from 0–44, with lower scores indicating more neurotoxic symptoms
  - Pain and NTx subscale scores were compared between treatment groups using a restricted maximum likelihood-based mixed model for repeated measures

Figure 2. ENDEAVOR Study Design



ISS, International Staging System; IV, intravenous; Kd56, carfilzomib (56 mg/m^2) and dexamethasone; PD, progressive disease; SC, subcutaneous; Vd, bortezomib and dexamethasone.

RESULTS

PN History

- In ASPIRE, a total of 228 patients (57.6%) in the KRd group and 214 (54.0%) in the Rd group had a history of nervous system disorders **(Table 1)**
  - In the KRd group, 144 patients (36.4%) had neuropathy of any grade at baseline and 22 (5.6%) had grade ≥2 neuropathy at baseline
  - In the Rd group, 137 patients (34.6%) had neuropathy of any grade at baseline and 24 (6.1%) had grade ≥2 neuropathy at baseline

Table 1. ASPIRE: History of Nervous System Disorders (ITT Population)

System Organ Class Preferred term, n (%)	KRd (n=396)	Rd (n=396)
Nervous system disorders	228 (57.6)	214 (54.0)
Peripheral neuropathy	78 (19.7)	63 (15.9)
Peripheral sensory neuropathy	53 (13.4)	53 (13.4)
Paresthesia	31 (7.8)	32 (8.1)
Polyneuropathy	25 (6.3)	21 (5.3)
Hypoesthesia	18 (4.5)	22 (5.6)
Neuralgia	16 (4.0)	16 (4.0)
Headache	15 (3.8)	9 (2.3)
Cerebrovascular accident	6 (1.5)	6 (1.5)

ITT, intention-to-treat; KRd, carfilzomib, lenalidomide, and dexamethasone; Rd, lenalidomide and dexamethasone.

- In ENDEAVOR, a total of 215 patients (46.3%) in the Kd56 group and 244 (52.5%) in the Vd group had a history of neuropathy **(Table 2)**
  - In the Kd56 group, 133 patients (28.7%) had grade 1 neuropathy at screening and 10 (2.2%) had grade 2 neuropathy at screening
  - In the Vd group, 159 patients (34.2%) had grade 1 neuropathy at screening and 10 (2.2%) had grade 2 neuropathy at screening

Table 2. ENDEAVOR: Baseline PN History (ITT Population)

	Kd56 (n=464)	Vd (n=465)
History of neuropathy, n (%)	215 (46.3)	244 (52.5)
Worst grade at any time, n (%)		
Grade 1	140 (30.2)	159 (34.2)
Grade 2	56 (12.1)	66 (14.2)
Grade 3	14 (3.0)	15 (3.2)
Grade 4	1 (0.2)	0
Unknown	4 (0.9)	4 (0.9)
Ongoing at screening, n (%)		
Grade 1	133 (28.7)	159 (34.2)
Grade 2	10 (2.2)	10 (2.2)

ITT, intention-to-treat; Kd56, carfilzomib (56 mg/m^2) and dexamethasone; PN, peripheral neuropathy; Vd, bortezomib and dexamethasone.

Rates of PN

- Neuropathy adverse events reported in ASPIRE and ENDEAVOR are summarized in **Table 3**
  - In ASPIRE, the rate of grade ≥2 PN (SMQN) was similar between treatment groups (8.9% [KRd] vs 8.0% [Rd]; odds ratio [OR], 1.13; 95% CI, 0.68–1.88; *P*=0.69)
  - In a secondary end point of ENDEAVOR, the proportion of patients who had grade ≥2 PN (SMQN) was significantly lower in the Kd56 group compared with the Vd group (6.0% [Kd] vs 32.0% [Vd]; OR, 0.137; 95% CI, 0.089–0.210; *P*<0.0001)
    - Of note, 79% of patients in the Vd group received subcutaneous bortezomib throughout study treatment

Table 3. ASPIRE and ENDEAVOR: Neuropathy Adverse Events by SMQN and Preferred Terms (Safety Population)

	ASPIRE				ENDEAVOR			
	KRd (n=392)		Rd (n=389)		Kd56 (n=463)		Vd (n=456)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Peripheral neuropathy (SMQN), n (%)	67 (17.1)	10 (2.6)	66 (17.0)	12 (3.1)	87 (18.8)	10 (2.2)	235 (51.5)	37 (8.1)
Peripheral neuropathy	29 (7.4)	6 (1.5)	27 (6.9)	6 (1.5)	43 (9.3)	6 (1.3)	121 (26.5)	24 (5.3)
Peripheral sensory neuropathy	22 (5.6)	2 (0.5)	27 (6.9)	0	27 (5.8)	1 (0.2)	67 (14.7)	6 (1.3)
Polyneuropathy	13 (3.3)	2 (0.5)	8 (2.1)	4 (1.0)	5 (1.1)	0	24 (5.3)	3 (0.7)
Neuralgia	4 (1.0)	1 (0.3)	7 (1.8)	2 (0.5)	9 (1.9)	3 (0.6)	70 (15.4)	7 (1.5)
Peripheral motor neuropathy	1 (0.3)	0	2 (0.5)	0	1 (0.2)	0	2 (0.4)	0
Sensorimotor disorder	1 (0.3)	0	0	0	0	0	0	0
Toxic neuropathy	1 (0.3)	0	0	0	0	0	1 (0.2)	0
Sensory loss	1 (0.3)	0	0	0	2 (0.4)	0	0	0
Peripheral sensorimotor neuropathy	0	0	0	0	1 (0.2)	0	2 (0.4)	0
Decreased vibratory sense	0	0	0	0	5 (1.1)	0	6 (1.3)	0
Amyotrophy	0	0	0	0	1 (0.2)	0	0	0
Sensory disturbance	0	0	0	0	1 (0.2)	0	0	0

Kd56, carfilzomib (56 mg/m^2) and dexamethasone; KRd, carfilzomib, lenalidomide, and dexamethasone; Rd, lenalidomide and dexamethasone; SMQN, Standardized MedDRA query, narrow scope; Vd, bortezomib and dexamethasone.

PROs Related to PN

- In a prespecified exploratory end point of ASPIRE, QLQ-C30 pain subscale scores were similar between the KRd and Rd groups **(Table 4)**
- In prespecified exploratory end points of ENDEAVOR, there were benefits in favor of the Kd56 group for the pain (*P*=0.02) and NTx subscales (*P*=0.0002)

Table 4. ASPIRE and ENDEAVOR: PROs Related to PN

	ASPIRE		ENDEAVOR	
	KRd	Rd	Kd56	Vd
PRO, LS mean difference				
Pain: QLQ-C30 subscale, ITT (95% CI)	−1.02 (−3.77 to 1.73) *P*=0.47		−2.35 (−4.30 to −0.39) *P*=0.0186	
Neurotoxicity: FACT/GOG-NTx subscale, safety population (95% CI)	—		0.84 (0.40 to 1.28) *P*=0.0002	

CI, confidence interval; FACT/GOG-NTx, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (subscale questionnaire); ITT, intention-to-treat; Kd56, carfilzomib (56 mg/m^2) and dexamethasone; KRd, carfilzomib, lenalidomide, and dexamethasone; LS, least squares; PN, peripheral neuropathy; PRO, patient-reported outcome; QLQ-C30, Quality of Life Questionnaire Core Module; Rd, lenalidomide and dexamethasone; Vd, bortezomib and dexamethasone.

CONCLUSIONS

- In ASPIRE, the PN rate was similar between the KRd and Rd groups
  - The addition of carfilzomib to Rd did not increase the incidence of PN
- In ENDEAVOR, Kd56 was associated with less PN compared with Vd
  - The majority of patients (79%) in the Vd group group received subcutaneous bortezomib throughout study treatment
  - The rate of grade ≥2 PN (secondary end point; grouped term) was significantly lower in the Kd56 group compared with the Vd group (6% vs 32%, respectively; *P*<0.0001)
- The clinical benefits of KRd vs Rd and Kd56 vs Vd were consistent, regardless of PN status at baseline
- Improved pain and neurotoxicity outcomes observed with Kd56 vs Vd may be attributed to better disease control and/or lower PN rates

PFS by PN History

- In ASPIRE, median PFS was longer with KRd vs Rd for patients who had grade ≥2 PN at baseline **(Table 5)**
- In ENDEAVOR, PFS was improved with Kd56 vs Vd for patients who had a history of PN

Table 5. ASPIRE and ENDEAVOR: PFS by PN Status at Baseline[a] (ITT Population)

	ASPIRE		ENDEAVOR	
	KRd	Rd	Kd	Vd
No PN, n	252	259	249	221
Median PFS (95% CI), months	31.0 (25.9–34.2)	16.8 (14.2–21.5)	17.7 (14.87–NE)	9.5 (7.96–12.14)
HR (95% CI)	0.610 (0.480–0.774)		0.52 (0.395–0.693)	
Any-grade PN, n	144	137	215	244
Median PFS (95% CI), months	23.2 (18.0–25.9)	17.6 (13.9–26.0)	18.7 (13.88–NE)	9.4 (7.53–10.39)
HR (95% CI)	0.947 (0.692–1.296)		0.54 (0.410–0.715)	
Grade ≥2 PN, n	22	24	71	81
Median PFS (95% CI), months	24.2 (19.6–NE)	14.8 (7.4–NE)	18.6 (10.20–NE)	5.6 (4.47–7.40)
HR (95% CI)	0.695 (0.321–1.507)		0.42 (0.266–0.677)	

[a]In ASPIRE, PN status at baseline was defined by the presence of neuropathy at baseline; in ENDEAVOR, PN status at baseline was defined by the presence of a history of PN.
CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; Kd56, carfilzomib (56 mg/m^2) and dexamethasone; KRd, carfilzomib, lenalidomide, and dexamethasone; NE, not estimable; PFS, progression-free survival; PN, peripheral neuropathy; Rd, lenalidomide and dexamethasone; Vd, bortezomib and dexamethasone.

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DISCLOSURES

RN has served in a consulting role for, participated in a speakers' bureau for, and received research funding from Celgene, Takeda, Amgen, Janssen, and BMS. VH has served in a consulting or advisory role for Amgen, Celgene, Janssen, and Takeda. PJH has served in an advisory role for Novartis, BMS, Amgen, Janssen, Takeda, and Celgene. DJW has received honoraria and research funding from and served in a consulting or advisory role for Amgen, BMS, Celgene, Janssen, and Takeda. LZ and KSI are stockholders and employees of Amgen. LR has received honoraria from Amgen, Celgene, and Janssen.

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Abstract #3120

Carfilzomib in Relapsed or Refractory Multiple Myeloma Patients with Early or Late Relapse Following Prior Therapy: A Subgroup Analysis of the Randomized Phase 3 ASPIRE and ENDEAVOR Trials

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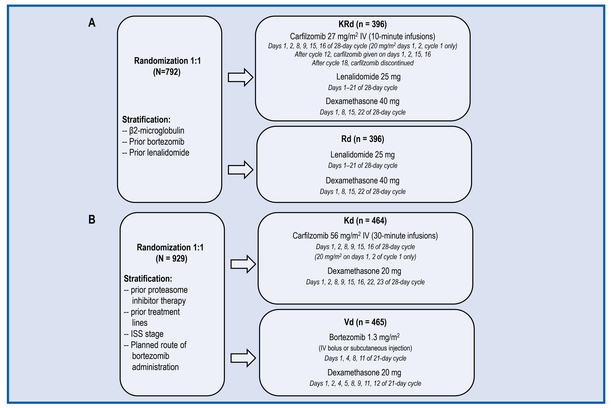
INTRODUCTION

- Carfilzomib is an irreversible proteasome inhibitor indicated for treatment of patients with relapsed or refractory multiple myeloma (RRMM)
- In the phase 3 ASPIRE trial, carfilzomib, lenalidomide and dexamethasone (KRd) improved progression-free survival (PFS) compared with lenalidomide and dexamethasone (Rd) in RRMM patients who received 1 to 3 prior lines of therapy (26.3 months vs 17.6 months; hazard ratio [HR]: 0.69; 95% confidence interval [CI]: 0.57–0.83; $P = 0.0001$)[1]
- In the phase 3 ENDEAVOR trial, carfilzomib and dexamethasone (Kd) improved PFS compared with bortezomib and dexamethasone (Vd) in RRMM patients who received 1 to 3 prior lines of therapy (18.7 months vs 9.4 months; HR 0.53, 95% CI 0.44–0.65; $P < 0.0001$)[2]
- Overall survival was improved in patients who received a carfilzomib-based regimen vs standard-of-care in both ASPIRE (48.3 months vs 40.4 months; HR 0.79; 95 % CI, 0.67–0.95) and ENDEAVOR (47.6 months vs 40.0 months; HR 0.79; 95% CI, 0.65–0.96)[3,4]
- Patients with MM who have early relapse following prior therapy typically have worse survival outcomes[5]
- In this post hoc subgroup analysis of ASPIRE and ENDEAVOR, we investigated the efficacy of carfilzomib among subgroups of patients who had early or late disease relapse following initiation of their most recent therapy

METHODS

- ASPIRE and ENDEAVOR were randomized, open-label, multicenter, phase 3 studies. Adult patients who had RRMM and received 1 to 3 prior lines of therapy were eligible
- Patients were randomized 1:1 to receive KRd or Rd in ASPIRE (Figure 1A) and 1:1 to receive Kd or Vd in ENDEAVOR (Figure 1B)
- Patients in ASPIRE and ENDEAVOR received treatment until unacceptable toxicity, progression, or withdrawal of consent. In ASPIRE carfilzomib was discontinued after cycle 18 (after which patients continued to receive only Rd)
- Data reported in this subgroup analysis were from preplanned interim analyses of ASPIRE (data cutoff date 16 June 2014) and ENDEAVOR (data cutoff date 10 November 2014)
- International Myeloma Working Group Uniform Response Criteria were used to evaluate disease response and progression.[6] The overall response rate (ORR) was defined as the percentage of patients achieving a best overall response of partial response (PR), very good partial response (VGPR), complete response (CR), or stringent complete response (sCR)
- The following subgroups were analyzed:
  (1) Patients who relapsed ≤ 1 year from starting the most recent prior line of therapy (early relapsers)
  (2) Patients who relapsed > 1 year from starting the most recent prior line of therapy (late relapsers)
- Relapse prior to trial entry was determined by investigator assessment (in ASPIRE patients were required to have symptomatic disease, and in ENDEAVOR patients were assessed for serological relapse/progression but were not required to have symptomatic disease)
- The *P* values reported for this post hoc analysis are descriptive

Figure 1. Design of Randomized Phase 3 Trials. (A) ASPIRE Trial (B) ENDEAVOR Trial



RESULTS

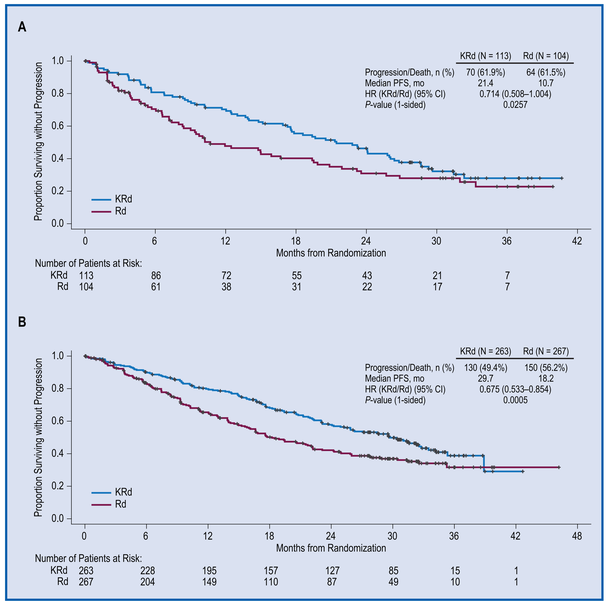
- In ASPIRE, relapse ≤ 1 year from initiating the most recent prior regimen occurred for 113/396 patients (29%) in the KRd arm and 104/396 patients (26%) in the Rd arm
- In ENDEAVOR, relapse ≤ 1 year from initiating the most recent prior regimen occurred for 123/464 patients (27%) in the Kd arm and 116/465 patients (25%) in the Vd arm

Table 1. Patient Baseline Demographic and Clinical Characteristics

	ASPIRE				ENDEAVOR			
	Early Relapsers		Late Relapsers		Early Relapsers		Late Relapsers	
	KRd (n = 113)	Rd (n = 104)	KRd (n = 263)	Rd (n = 267)	Kd (n = 123)	Vd (n = 116)	Kd (n = 335)	Vd (n = 340)
Age, median years (range)	64.0 (41–85)	65.0 (40–87)	64.0 (38–87)	65.0 (31–91)	64.0 (35–82)	65.0 (42–85)	65.0 (36–89)	66.0 (30–88)
Cytogenetic risk by FISH at study entry, n (%)								
High risk	14 (12.4)	16 (15.4)	30 (11.4)	31 (11.6)	35 (28.5)	40 (34.5)	62 (18.5)	72 (21.2)
Standard risk	40 (35.4)	33 (31.7)	101 (38.4)	127 (47.6)	67 (54.5)	64 (55.2)	214 (63.9)	221 (65.0)
Unknown/missing	59 (52.2)	55 (52.9)	132 (50.2)	109 (40.8)	21 (17.1)	12 (10.3)	59 (17.6)	47 (13.8)
Serum β_2-microglobulin level, n (%)								
< 2.5 mg/L (ASPIRE)/ < 3.5 mg/L (ENDEAVOR)	20 (17.7)	14 (13.5)	52 (19.8)	55 (20.6)	53 (43.1)	44 (37.9)	163 (48.7)	167 (49.1)
≥ 2.5 mg/L (ASPIRE)/ ≥ 3.5 mg/L (ENDEAVOR)	93 (82.3)	90 (86.5)	211 (80.2)	212 (79.4)	70 (56.9)	72 (62.1)	172 (51.3)	173 (50.9)
Number of prior regimens, n (%)								
1	37 (32.7)	26 (25.0)	147 (55.9)	130 (48.7)	31 (25.2)	24 (20.7)	200 (59.7)	202 (59.4)
2	40 (35.4)	34 (32.7)	69 (26.2)	93 (34.8)	61 (49.6)	56 (48.3)	93 (27.8)	87 (25.6)
3	35 (31.0)	43 (41.3)	47 (17.9)	44 (16.5)	31 (25.2)	35 (30.2)	42 (12.5)	51 (15.0)
Prior therapy, n (%)								
Bortezomib	84 (74.3)	78 (75.0)	160 (60.8)	167 (62.5)	65 (52.8)	66 (56.9)	182 (54.3)	182 (53.5)
Lenalidomide	24 (21.2)	26 (25.0)	51 (19.4)	48 (18.0)	65 (52.8)	70 (60.3)	112 (33.4)	104 (30.6)

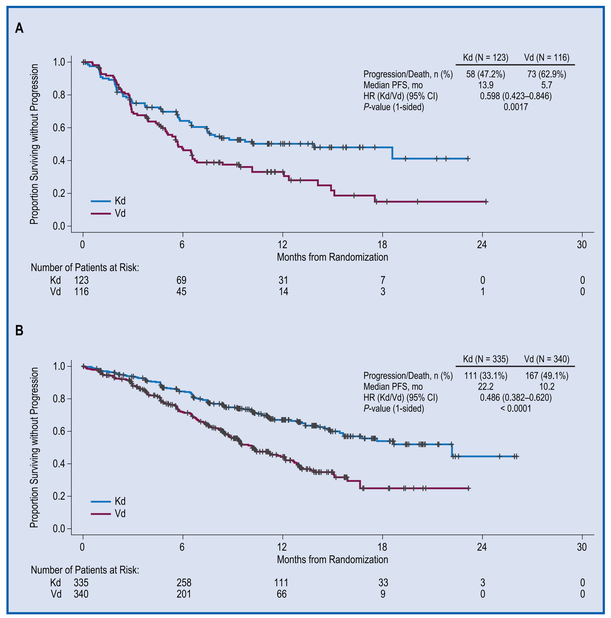
High-risk patients had genetic subtypes t(4; 14), t(14;16), or deletion 17p, while standard-risk patients did not.

Figure 2. Progression-free Survival in the ASPIRE Trial. (A) Early Relapsers (B) Late Relapsers



- In ASPIRE, the median PFS for early relapsers was 21.4 months (95% CI: 17.3–26.1) for KRd vs 10.7 months (95% CI: 8.3–19.4) for Rd (HR: 0.714; 95% CI: 0.508–1.004; $P = 0.0257$) (Figure 2A)
- The median PFS for late relapsers was 29.7 months (95% CI: 24.9–33.5) for KRd vs 18.2 months (95% CI: 15.6–22.2) for Rd (HR: 0.675; 95% CI: 0.533–0.854; $P = 0.0005$) (Figure 2B)

Figure 3. Progression-free Survival in the ENDEAVOR Trial. (A) Early Relapsers (B) Late Relapsers



- In ENDEAVOR, the median PFS for early relapsers was 13.9 months (95% CI: 7.4–not evaluable [NE]) for Kd vs 5.7 months (95% CI: 4.8–6.7) for Vd (HR: 0.598; 95% CI: 0.423–0.846; $P = 0.0017$) (Figure 3A)
- The median PFS for late relapsers was 22.2 months (95% CI: 15.7–NE) for Kd vs 10.2 months (95% CI: 9.0–12.1) for Vd (HR: 0.486; 95% CI: 0.382–0.620; $P < 0.0001$) (Figure 3B)

Table 2. Best Overall Response and Overall Response Rate

	ASPIRE				ENDEAVOR			
	Early Relapsers		Late Relapsers		Early Relapsers		Late Relapsers	
	KRd (n = 113)	Rd (n = 104)	KRd (n = 263)	Rd (n = 267)	Kd (n = 123)	Vd (n = 116)	Kd (n = 335)	Vd (n = 340)
Best overall response, n (%)								
Stringent complete response	10 (8.8)	4 (3.8)	42 (16.0)	12 (4.5)	1 (0.8)	3 (2.6)	7 (2.1)	6 (1.8)
Complete response	15 (13.3)	4 (3.8)	55 (20.9)	15 (5.6)	7 (5.7)	1 (0.9)	43 (12.8)	19 (5.6)
Very good partial response	47 (41.6)	24 (23.1)	97 (36.9)	89 (33.3)	42 (34.1)	20 (17.2)	148 (44.2)	80 (23.5)
Partial response	22 (19.5)	25 (24.0)	40 (15.2)	70 (26.2)	27 (22.0)	33 (28.4)	76 (22.7)	121 (35.6)
Overall response rate, % (95% CI)	83.2 (75.0–89.6)	54.8 (44.7–64.6)	89.0 (84.5–92.5)	69.7 (63.8–75.1)	63.4 (54.3–71.9)	49.1 (39.7–58.6)	81.8 (77.2–85.8)	66.8 (61.5–71.8)
Complete response or better, n (%)	25 (22.1)	8 (7.7)	97 (36.9)	27 (10.1)	8 (6.5)	4 (3.4)	50 (14.9)	25 (7.4)

- In ASPIRE, the ORR (KRd vs Rd) was 83.2% vs 54.8% for early relapsers and 89.0% vs 69.7% for late relapsers (Table 2)
- In ENDEAVOR, the ORR (Kd vs Vd) was 63.4% vs 49.1% for early relapsers and 81.8% vs 66.8% for late relapsers (Table 2)

Table 3. Treatment-emergent Adverse Events and Treatment Discontinuation Due to Adverse Events (Safety Population)

	ASPIRE				ENDEAVOR			
	Early Relapsers		Late Relapsers		Early Relapsers		Late Relapsers	
	KRd (n = 112)	Rd (n = 100)	KRd (n = 260)	Rd (n = 264)	Kd (n = 122)	Vd (n = 114)	Kd (n = 335)	Vd (n = 333)
Any-grade adverse event, n (%)	111 (99.1)	96 (96.0)	251 (96.5)	258 (97.7)	119 (97.5)	112 (98.2)	330 (98.5)	326 (97.9)
Grade ≥ 3 adverse event, n (%)	92 (82.1)	81 (81.0)	221 (85.0)	212 (80.3)	84 (68.9)	85 (74.6)	250 (74.6)	215 (64.6)
Adverse event leading to treatment discontinuation, n (%)	33 (29.5)	29 (29.0)	66 (25.4)	62 (23.5)	25 (20.5)	20 (17.5)	65 (19.4)	74 (22.2)
Fatal adverse event, n (%)	17 (15.2)	13 (13.0)	19 (7.3)	22 (8.3)	9 (7.4)	9 (7.9)	15 (4.5)	12 (3.6)

- In ASPIRE, rates of grade ≥ 3 adverse events (KRd vs Rd) for early relapsers were 82.1% vs 81.0% and for late relapsers were 85.0% vs 80.3% (Table 3)
- In ENDEAVOR, rates of grade ≥ 3 adverse events (Kd vs Vd) for early relapsers were 68.9% vs 74.6% and for late relapsers were 74.6% vs 64.6% (Table 3)

CONCLUSIONS

- In both trials, early relapsers tended more often to have 3 prior treatment lines and more prior treatment with bortezomib and lenalidomide compared to late relapsers. In ENDEAVOR, the proportion of early relapsers with high cytogenetic risk was also higher compared to late relapsers
- Patients with RRMM who received carfilzomib-based therapy had improved PFS compared with standard-of-care, in both subgroups of early relapsers and late relapsers
  - In ASPIRE, median PFS was improved by 10.7 months among early relapsers and by 11.5 months among late relapsers receiving KRd vs Rd
  - In ENDEAVOR, median PFS was improved by 8.2 months among early relapsers and by 12.0 months among late relapsers receiving Kd vs Vd
- As expected, early relapsers had shorter PFS and lower ORRs compared to late relapsers
- Safety profiles for the early relapser and late relapser subgroups were comparable to those previously reported for the ASPIRE and ENDEAVOR trials[1,2]
- In conclusion, these results from ASPIRE and ENDEAVOR demonstrate that patients with RRMM benefitted from carfilzomib-containing treatment (KRd or Kd) compared with standard-of-care (Rd or Vd), regardless of whether they had early or late relapse following most recent prior therapy

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DISCLOSURES

MVM has received honoraria from Janssen, Celgene, Amgen, and Takeda. HG has received consulting fees from Amgen, Bristol-Myers Squibb, Celgene, Janssen, Novartis, and Takeda; honoraria from Bristol-Myers Squibb, Celgene, Chugai, Janssen, and Novartis; and research funding from Bristol-Myers Squibb, Celgene, Chugai, Janssen, and Novartis. JS-M has received consulting fees from Bristol-Myers Squibb, Celgene, Janssen, Millennium, Merck Sharp & Dohme, Novartis, Sanofi, Roche, and Amgen. JM reports that AbbVie, Celgene, and Sanofi have contracted research with Mayo Clinic. LD is an employee of and owns stock in Amgen. LZ is an employee of and owns stock in Amgen. MO is an employee of and owns stock in Amgen. JB is an employee of and owns stock in Amgen. ZS is an employee of Amgen Europe GmbH and owns stock in Amgen. XL has received honoraria and consulting fees from and is on advisory committees for Janssen, Celgene, Bristol-Myers Squibb, Takeda, Amgen, Merck, Novartis, Pierre Fabre, AbbVie, and Sanofi.

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Superior Efficacy of Carfilzomib and Dexamethasone (Kd56) vs Bortezomib and Dexamethasone (Vd) in Multiple Myeloma (MM) Patients With Moderate or Serious Renal Failure: A Subgroup Analysis of the Phase 3 ENDEAVOR study

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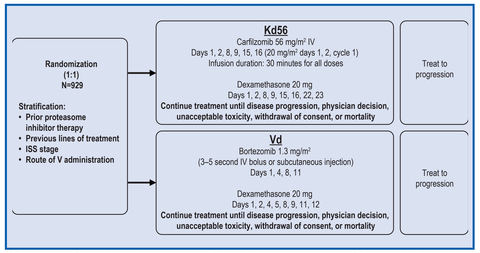
INTRODUCTION

- Carfilzomib, a second-generation selective proteasome inhibitor, is approved in the United States and Europe for the treatment of relapsed or refractory multiple myeloma (RRMM) in combination with lenalidomide plus dexamethasone or with dexamethasone alone[1]
- In the ENDEAVOR study, carfilzomib (56 mg/m^2) and dexamethasone (Kd56) demonstrated clinically and statistically significant improvement compared with bortezomib and dexamethasone (Vd) in PFS (primary endpoint; median 18.7 vs 9.4 months; hazard ratio [HR], 0.53; 95% confidence interval [CI], 0.44–0.65; 1-sided P<0.0001)[2] and OS (secondary endpoint; median, 47.6 months vs 40.0 months; HR, 0.791; 95% CI, 0.648–0.964; 1-sided P=0.010)[3]
- Renal impairment is a common complication of MM and is associated with poor prognosis and shorter survival in patients with MM[4,5]
- Carfilzomib may be administered in patients with various degrees of renal impairment, including patients on dialysis, without starting-dose adjustment[6]
- Here, we present a post-hoc, exploratory subgroup analysis from the ENDEAVOR study to evaluate Kd56 and Vd in patients with impaired renal function

METHODS

- ENDEAVOR was a phase 3, randomized, multicenter, open-label study. Adults with RRMM (1–3 prior regimens) and creatinine clearance (CrCL) ≥15 mL/min were eligible
- Patients were randomized 1:1 to receive Kd56 or Vd, and treatment was given until disease progression, physician decision, unacceptable toxicity, withdrawal of consent, or mortality **(Figure 1)**
- The present analyses examined efficacy and safety outcomes in patients grouped according to baseline renal function (CrCL ≥15 to <50, 50 to <80, and ≥80 mL/min)
- Based on International Myeloma Working Group criteria,[7] a complete renal response was defined as CrCL ≥60 mL/min in any 2 consecutive study visits for patients who had baseline CrCL <50 mL/min
  - The Cockcroft-Gault (C-G) formula was used to calculate baseline and on-study renal function. This formula was calculated using actual body weight
    - Although the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula is preferred over the C-G equation in evaluation of renal function in MM patients,[7] the analysis reported here was done using the C-G equation. The CKD-EPI equation requires data on race. Use of the C-G equation allowed all subject data to be used, whereas use of the CKD-EPI equation would not have supported analysis of the entire ENDEAVOR patient population, due to missing data on race

Figure 1. ENDEAVOR Study Design



ISS, International Staging System; IV, intravenous; Kd56, carfilzomib and dexamethasone; PD, progression disease; V, bortezomib; Vd, bortezomib and dexamethasone.

RESULTS

- The intent-to-treat (ITT) population included 929 patients enrolled at sites in North and South America, Eastern and Western Europe, and Asia-Pacific:
  - CrCL ≥15 to <50 mL/min: Kd56, n=85; Vd, n=99
  - CrCL 50 to <80 mL/min: Kd56, n=186; Vd, n=177
  - CrCL ≥80 mL/min: Kd56, n=193; Vd, n=189
- Demographics and baseline disease characteristics were generally balanced between arms within a CrCL subgroup, with the exception of the CrCL ≥15 to <50 mL/min subgroup where more patients (≥ 10% difference) had high risk cytogenetics and were 65–74 years of age in the Vd arm **(Table 1)**
  - In the CrCL ≥15 to <50 mL/min subgroup, the proportion of patients aged ≥65 years was similar between treatment arms (Kd56, 74.1%; Vd, 77.8%)
- Overall, a higher percentage of patients with impaired renal function (CrCL ≥15 to <50 mL/min) were older and had more severe disease (International Staging System stage 3) compared with other CrCL subgroups

Table 1. Patient Demographics and Baseline Disease Characteristics

	CrCL ≥15 to <50 mL/min		CrCL 50 to <80 mL/min		CrCL ≥80 mL/min	
	Kd56 (n=85)	Vd (n=99)	Kd56 (n=186)	Vd (n=177)	Kd56 (n=193)	Vd (n=189)
Age						
Median years (range)	72.0 (41–89)	72.0 (45–86)	68.0 (39–89)	68.0 (44–88)	60.0 (35–81)	61.0 (30–81)
<65 years	22 (25.9)	22 (22.2)	64 (34.4)	53 (29.9)	137 (71.0)	135 (71.4)
65–74 years	28 (32.9)	44 (44.4)	85 (45.7)	97 (54.8)	51 (26.4)	48 (25.4)
≥75 years	35 (41.2)	33 (33.3)	37 (19.9)	27 (15.3)	5 (2.6)	6 (3.2)
Cytogenetic risk by FISH at study entry, n (%)[a]						
High risk	11 (12.9)	26 (26.3)	45 (24.2)	41 (23.2)	41 (21.2)	46 (24.3)
Standard risk	55 (64.7)	61 (61.6)	111 (59.7)	117 (66.1)	118 (61.1)	113 (59.8)
Unknown/missing	19 (22.4)	12 (12.1)	30 (16.1)	19 (10.7)	34 (17.6)	30 (15.9)
ISS stage at baseline, n (%)						
Stage 1	11 (12.9)	9 (9.1)	76 (40.9)	69 (39.0)	125 (64.8)	127 (67.2)
Stage 2	28 (32.9)	28 (28.3)	66 (35.5)	75 (42.4)	45 (23.3)	48 (25.4)
Stage 3	46 (54.1)	62 (62.6)	44 (23.7)	33 (18.6)	23 (11.9)	14 (7.4)
Number of prior regimens						
1	39 (45.9)	43 (43.4)	96 (51.6)	85 (48.0)	96 (49.7)	101 (53.4)
2-3	46 (54.1)	56 (56.6)	90 (48.4)	92 (52.0)	97 (50.3)	88 (46.6)

[a]High-risk subjects have genetic subtypes t(4;14), t(14;16), or del(17p), while standard-risk subjects do not. The unknown risk group includes subjects who have FISH assessment, but the result of one or more genetic subtypes are not available.
CrCL, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in-situ hybridization; ISS, International Staging System; Kd56, carfilzomib and dexamethasone; Vd, bortezomib and dexamethasone.

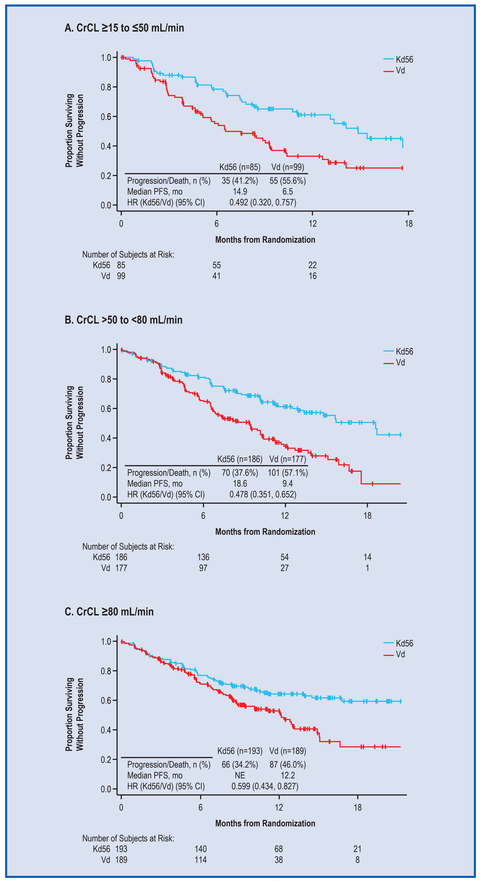
- PFS and OS were superior with Kd56 vs Vd within each renal subgroup **(Table 2 and Figures 2 and 3)**
  - For the CrCL ≥15 to <50 mL/min group, median PFS was 14.9 months for Kd56 vs 6.5 months for Vd (HR [95% CI], 0.49 [0.320–0.757]). For the CrCL 50 to <80 mL/min group, these values were 18.6 months vs 9.4 months (HR [95% CI], 0.48 [0.351–0.652]) and for the CrCL ≥80 mL/min group, not reached (NR) vs 12.2 months (HR [95% CI], 0.60 [0.434–0.827])
  - For the CrCL ≥15 to <50 mL/min group, median OS was 40.5 months (Kd56) vs 23.9 months (Vd; HR [95% CI], 0.67 [0.439–1.020]). For the CrCL 50 to <80 mL/min group, these values were NR vs 35.9 months (HR [95% CI], 0.84 [0.619–1.137]) and for the CrCL ≥80 mL/min group, 47.6 months vs 42.2 months (HR [95% CI], 0.84 [0.604–1.168])
- ORRs were higher in the Kd56 arm compared with the Vd arm in each renal subgroup **(Table 2)**
- The median duration of response was longer with Kd56 than with Vd in the overall population and across renal subgroups
- In patients with CrCL ≥15 to <50 mL/min, complete renal response rates were comparable between the 2 arms and were 15.3% for Kd56 and 14.1% for Vd

Table 2. Efficacy Outcomes by Renal Impairment Subgroup

	CrCL ≥15 to <50 mL/min		CrCL 50 to <80 mL/min		CrCL ≥80 mL/min	
	Kd56 (n=85)	Vd (n=99)	Kd56 (n=186)	Vd (n=177)	Kd56 (n=193)	Vd (n=189)
Median PFS, months[a]	14.9	6.5	18.6	9.4	Not reached	12.2
HR for Kd56 vs Vd (95% CI)	0.49 (0.320–0.757)		0.48 (0.351–0.652)		0.60 (0.434–0.827)	
Median OS, months	40.5	23.9	Not reached	35.9	47.6	42.2
HR for Kd56 vs Vd (95% CI)	0.67 (0.439–1.020)		0.84 (0.619–1.137)		0.84 (0.604–1.168)	
ORR, %[a]	74.1	49.5	78.5	69.5	76.7	63.0
Odds ratio (95% CI)	2.922 (1.564–5.460)		1.602 (0.997–2.574)		1.935 (1.239 –3.021)	
CR+, %[a]	8.2	4.0	9.1	7.3	17.6	6.3
VGPR+, %[a]	51.8	28.3	55.4	26.0	54.4	31.2
Median DOR, months[a]	16.6	9.3	17.6	9.3	Not reached	14.0
Complete renal response, %	15.3	14.1	—	—	—	—

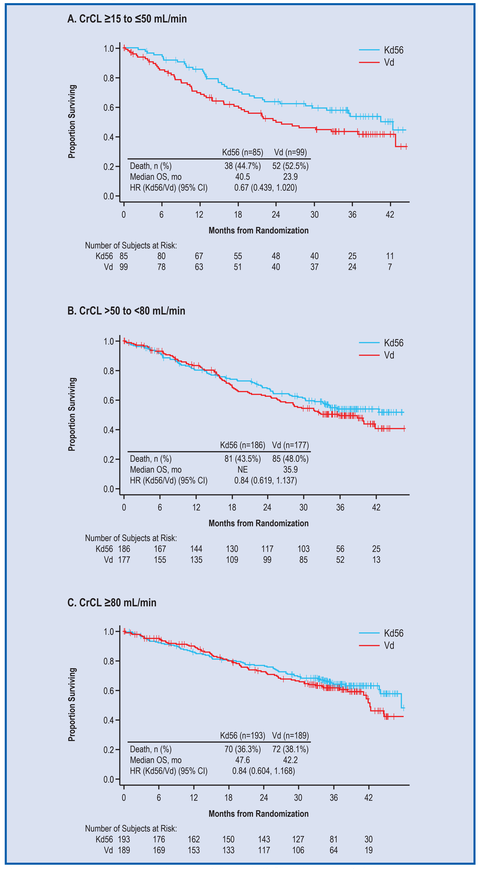
[a]Data are from the primary analysis data cut.
CI, confidence interval; CR+, complete response or better, CrCL, creatinine clearance; DOR, duration of response; HR, hazard ratio; Kd56, carfilzomib and dexamethasone; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Vd, bortezomib and dexamethasone; VGPR+, very good partial response or better.

Figure 2. Kaplan-Meier PFS Curves for Kd56 and Vd by Renal Impairment Subgroup



Kaplan-Meier curves were displayed until there were ≤10 subjects (Kd56 and Vd combined) at risk.
CI, confidence interval; CrCL, creatinine clearance; HR, hazard ratio; Kd56, carfilzomib and dexamethasone; PFS, progression-free survival; Vd, bortezomib and dexamethasone.

Figure 3. Kaplan-Meier OS Curves for Kd56 and Vd by Renal Impairment Subgroup



Kaplan-Meier curves were displayed until there were ≤10 subjects (Kd56 and Vd combined) at risk.
CI, confidence interval; CrCL, creatinine clearance; HR, hazard ratio; Kd56, carfilzomib and dexamethasone; OS, overall survival; Vd, bortezomib and dexamethasone.

- The median duration of treatment was longer and the median number of cycles received were higher with Kd56 vs Vd across all CrCL subgroups
- Grade ≥3 adverse event (AE) rates for Kd56 vs Vd were 87.1% vs 79.4% (CrCL ≥15 to <50 mL/min), 83.9% vs 71.8% (CrCL 50 to <80 mL/min), and 76.6% vs 65.9% (CrCL ≥80 mL/min)
- Rates of grade ≥3 acute renal failure, hypertension, cardiac failure, and dyspnea were higher with Kd56 vs Vd across renal subgroups, while grade ≥3 PN rates were lower in the Kd56 arm compared with Vd arm across renal subgroups **(Table 3)**
- AEs were not adjusted for exposure

Table 3. Safety Outcomes by Renal Impairment Subgroup

	CrCL ≥15 to <50 mL/min		CrCL 50 to <80 mL/min		CrCL ≥80 mL/min	
	Kd56 (n=85)	Vd (n=97)	Kd56 (n=186)	Vd (n=174)	Kd56 (n=192)	Vd (n=185)
Median (IQR) duration of treatment, weeks	36 (18–68)	21 (12–34)	50 (25–87)	27 (15–45)	52 (26–103)	31 (17–60)
Median (IQR) number of cycles received, n	9 (4–17)	7 (4–11)	12 (6–21)	8 (5–13)	13 (7–25)	10 (6–19)
Patients with AEs leading to carfilzomib or bortezomib discontinuation, n (%)	27 (31.8)	23 (23.7)	45 (24.2)	40 (23.0)	44 (22.9)	36 (19.5)
Treatment-emergent grade ≥3 AEs of interest, n (%)[a]						
Hypertension, n (%)	12 (14.1)	3 (3.1)	25 (13.4)	7 (4.0)	30 (15.6)	5 (2.7)
Peripheral neuropathy, n (%)	0	4 (4.1)	5 (2.7)	16 (9.2)	1 (0.5)	8 (4.3)
Dyspnea, n (%)	8 (9.4)	2 (2.1)	12 (6.5)	2 (1.1)	9 (4.7)	6 (3.2)
Cardiac failure, n (%)	4 (4.7)	0	7 (3.8)	1 (0.6)	2 (1.0)	2 (1.1)
Acute renal failure, n (%)	3 (3.5)	2 (2.1)	4 (2.2)	2 (1.1)	5 (2.6)	3 (1.6)

AEs were not adjusted for exposure.
[a]Preferred term.
AE, adverse event; CrCL, creatinine clearance; IQR, interquartile range; Kd56, carfilzomib and dexamethasone; Vd, bortezomib and dexamethasone.

CONCLUSIONS

- **ENDEAVOR is the largest randomized trial in RRMM to have included patients with severe renal impairment**
- **Clinically meaningful improvements in PFS and OS were observed with Kd56 vs Vd in all CrCL subgroups, including patients with severe renal impairment**
  - **CrCL ≥15 to <50 mL/min = 8.4-month improvement in median PFS (HR, 0.49; 95% CI, 0.32 to 0.76) and 16.6-month improvement in median OS (HR, 0.67; 95% CI, 0.44 to 1.02)**
    - **Patients treated with Kd56 also had a higher ORR than those treated with Vd (74.1% vs 49.5%; odds ratio, 2.9)**
  - **CrCL 50 to <80 mL/min = 9.2-month improvement in median PFS (HR, 0.48; 95% CI, 0.35 to 0.65) and improvement in median OS not estimable (HR, 0.84; 95% CI, 0.62 to 1.14)**
  - **CrCL ≥80 mL/min = improvement in median PFS not estimable (HR, 0.60; 95% CI, 0.43 to 0.83) and 5.4-month improvement in median OS (HR, 0.84; 95% CI, 0.60 to 1.17)**
- **Patients with severe renal failure (CrCL ≥15 to <50 mL/min) treated with Kd56 had median OS of 40.5 months, which is higher than expected for this patient population and much closer to that observed in patients with normal renal function (CrCL ≥80 mL/min) when compared with the median OS observed for patients with severe renal failure treated with Vd, indicating Kd56 may overcome the poor prognosis of baseline renal impairment**
- **The safety profile was consistent with the findings from the previous interim analysis, with no new safety signals identified[8]**
  - **In general, a greater percentage of patients in the CrCL ≥15 to <50 mL group reported grade ≥3 AEs compared with the other groups**
- **Overall, these data suggest that Kd56 has a favorable benefit-risk profile and should be considered as the new standard of care in pts with RRMM, regardless of baseline renal function**

CONFLICT OF INTEREST DISCLOSURE

MD served as a consultant for Celgene, Janssen, Amgen Inc., Novartis, and Takeda. **DS** served as a consultant for and received honoraria from Celgene, Takeda, Amgen, Novartis, and BMS. **DJW** served as a consultant for, and received research funding and honoraria from, Amgen, BMS, Celgene, Janssen, Novartis, and Takeda. **RB** served on advisory boards for Pfizer Inc. and Sandoz. **ZY, ASK, KI,** and **KM** are employees and stock/equity owners of Amgen. **HL** served as a consultant/advisory for Takeda, Amgen, and Janssen; served on the speakers' bureau for Celgene, Takeda, Amgen, BMS, and Janssen; and received research funding from Takeda and Amgen. **RN** received personal fees from Celgene and Millennium.

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