

# Improvement in Overall Survival With Carfilzomib, Lenalidomide, and Dexamethasone in Patients With Relapsed or Refractory Multiple Myeloma

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## A B S T R A C T

### Purpose

In the ASPIRE study of carfilzomib, lenalidomide, and dexamethasone (KRd) versus lenalidomide plus dexamethasone (Rd) in patients with relapsed or refractory multiple myeloma, progression-free survival was significantly improved in the carfilzomib group (hazard ratio, 0.69; two-sided  $P < .001$ ). This prespecified analysis reports final overall survival (OS) data and updated safety results.

### Patients and Methods

Adults with relapsed multiple myeloma (one to three prior lines of therapy) were eligible and randomly assigned at a one-to-one ratio to receive KRd or Rd in 28-day cycles until withdrawal of consent, disease progression, or occurrence of unacceptable toxicity. After 18 cycles, all patients received Rd only. Progression-free survival was the primary end point; OS was a key secondary end point. OS was compared between treatment arms using a stratified log-rank test.

### Results

Median OS was 48.3 months (95% CI, 42.4 to 52.8 months) for KRd versus 40.4 months (95% CI, 33.6 to 44.4 months) for Rd (hazard ratio, 0.79; 95% CI, 0.67 to 0.95; one-sided  $P = .0045$ ). In patients receiving one prior line of therapy, median OS was 11.4 months longer for KRd versus Rd; it was 6.5 months longer for KRd versus Rd among patients receiving  $\geq$  two prior lines of therapy. Rates of treatment discontinuation because of adverse events (AEs) were 19.9% (KRd) and 21.5% (Rd). Grade  $\geq$  3 AE rates were 87.0% (KRd) and 83.3% (Rd). Selected grade  $\geq$  3 AEs of interest (grouped terms; KRd v Rd) included acute renal failure (3.8% v 3.3%), cardiac failure (4.3% v 2.1%), ischemic heart disease (3.8% v 2.3%), hypertension (6.4% v 2.3%), hematopoietic thrombocytopenia (20.2% v 14.9%), and peripheral neuropathy (2.8% v 3.1%).

### Conclusion

KRd demonstrated a statistically significant and clinically meaningful reduction in the risk of death versus Rd, improving survival by 7.9 months. The KRd efficacy advantage is most pronounced at first relapse.

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## INTRODUCTION

Although the introduction of new therapies such as proteasome inhibitors and immunomodulatory agents has resulted in improved outcomes in multiple myeloma (MM),<sup>1-3</sup> most patients relapse after initial therapy. Upon relapse, patients face poor outcomes, which worsen with subsequent lines of therapy, as treatment resistance develops<sup>4</sup> and disease- and treatment-related complications<sup>5</sup> increase.

Because MM remains an incurable disease, extending overall survival (OS) in the relapsed

setting is a therapeutic goal. Recent phase III trials in relapsed or refractory MM (RRMM) have used progression-free survival (PFS) as the primary end point. With an increasing number of salvage therapy options, OS is being extended, and confounding by subsequent therapies may become an issue. Only one study to date, the phase III trial ENDEAVOR (RandomizEd, OpeN Label, Phase 3 Study of Carfilzomib Plus DEXamethAsone Vs Bortezomib Plus DexamethAsone in Patients With Relapsed Multiple Myeloma),<sup>6</sup> has demonstrated statistically significant prolongation of OS for a novel therapy versus a recent standard of care. In ENDEAVOR, patients treated with carfilzomib and

## ASSOCIATED CONTENT



Appendix  
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Data Supplement  
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dexamethasone achieved a significant 7.6-month median OS improvement versus patients treated with bortezomib and dexamethasone (Vd; median, 47.6 v 40.0 months; hazard ratio [HR], 0.791; 95% CI, 0.648 to 0.964; one-sided  $P = .010$ ).<sup>6</sup>

At the interim analysis of the randomized phase III trial ASPIRE (Carfilzomib, Lenalidomide, and Dexamethasone versus Lenalidomide and Dexamethasone for the treatment of Patients with Relapsed Multiple Myeloma), the addition of carfilzomib to lenalidomide plus dexamethasone (KRd) significantly improved PFS compared with lenalidomide plus dexamethasone alone (Rd) in patients with RRMM (median, 26.3 v 17.6 months; HR, 0.69; 95% CI, 0.57 to 0.83; two-sided  $P < .001$ ).<sup>7</sup> Overall response rate (ORR; 87.1% v 66.7%),  $\geq$  complete response rate (31.8% v 9.3%), and median duration of response (28.6 v 21.2 months) were also improved.<sup>7</sup> Secondary analyses showed that the benefit of KRd was consistent, regardless of age, number of prior lines of therapy, previous treatment, or cytogenetic risk.<sup>8-11</sup> Despite prolonged treatment exposure in the KRd group, rates of discontinuation because of adverse events (AEs) were lower with KRd, and the frequency of AE-related deaths was identical in the two groups.<sup>7</sup> Finally, KRd resulted in superior health-related quality of life (HRQoL), with no detrimental impact on other patient-reported outcomes.<sup>12</sup> Here we report results from the prospectively planned final analysis of OS in ASPIRE.

## PATIENTS AND METHODS

### Study Design and Patients

The ASPIRE trial design has been described previously.<sup>7</sup> ASPIRE was a randomized, open-label, multicenter, phase III study of adults with relapsed MM who had received one to three prior lines of therapy. Additional eligibility criteria are described in the Appendix (online only). The study protocol was approved by institutional review boards of participating institutions. Investigators obtained written informed consent from all patients.

### Random Assignment

Patients were randomly assigned at a one-to-one ratio to receive KRd or Rd in 28-day cycles until withdrawal of consent, disease progression, or occurrence of unacceptable toxicity. Random assignment was stratified according to  $\beta_2$ -microglobulin level ( $< 2.5$  v  $\geq 2.5$  mg/L) and previous bortezomib (no v yes) or lenalidomide therapy (no v yes).

### Treatment

Carfilzomib (20 mg/m<sup>2</sup> on days 1 and 2 of cycle one; 27 mg/m<sup>2</sup> thereafter) was administered as a 10-minute infusion on days 1, 2, 8, 9, 15, and 16 during cycles one to 12 and on days 1, 2, 15, and 16 in cycles 13 to 18. Lenalidomide (25 mg) was administered on days 1 to 21 and dexamethasone (40 mg) on days 1, 8, 15, and 22. Per protocol, carfilzomib was stopped after 18 cycles for patients randomly assigned to KRd because of the limited long-term safety data available when ASPIRE was initiated. Subsequently, these patients received Rd only.

### Assessments

Assessments of disease progression were performed using International Myeloma Working Group Uniform Response Criteria.<sup>13</sup> Upon treatment discontinuation, patients were observed for disease and survival status every 3 months for 1 year from treatment discontinuation and every

6 months thereafter until the patient withdrew consent, was lost to follow-up, or died.

The Common Terminology Criteria for AEs (version 4.0) was used to describe AEs. Data on AEs were collected until 30 days after last dose of study drug or initiation of new anticancer therapy, whichever occurred first. Treatment-emergent AEs (TEAEs) were defined as AEs that started on or after first day study treatment was administered and within 30 days of last administration of study treatment.

### Outcomes

The primary end point of ASPIRE was PFS based on assessments by an independent review committee. OS was a key secondary end point.

At the time of the interim analysis, OS data favored KRd; however, these results did not cross the prespecified stopping boundary for OS at the interim analysis, and patients continued to be observed for OS events for the final OS analysis.<sup>7</sup> Per protocol, inferential testing for the secondary efficacy end points were to be performed sequentially in the following order: OS, ORR, disease control rate, and HRQoL.

If OS were significant at the final analysis, test results of ORR, disease control rate, and HRQoL obtained at interim would be used to determine statistical significance. PFS outcomes as assessed by investigators served as a supplemental secondary analysis. Safety data continued to be collected after the interim analysis, and updated results are reported here.

### Statistical Analysis

OS was evaluated using an O'Brien-Fleming group sequential monitoring plan, with preplanned interim and final analyses, to ensure a one-sided type I error rate of .025. The final OS analysis was planned to be performed after 510 deaths had occurred, which would provide 85% power to detect, with a one-sided significance level of .025, a 23.5% reduction in the risk of death for KRd versus Rd. An O'Brien-Fleming stopping boundary for efficacy was calculated using a Lan-DeMets  $\alpha$  spending function.<sup>14,15</sup>

OS, survival beyond progression, and time to next treatment were analyzed using the Kaplan-Meier method. The between-treatment OS comparison used a log-rank test stratified with the randomization factors. OS HRs were estimated with a Cox proportional hazards model using the same randomization stratification factors. The piecewise Cox model was based on Collett.<sup>16</sup>

Subgroup analyses were conducted to evaluate OS by number of prior lines of therapy, cytogenetic risk,<sup>8</sup> prior bortezomib exposure at first relapse, transplantation at first relapse, Revised International Staging System (R-ISS) stage,<sup>17</sup> age, creatinine clearance (CrCL), Eastern Cooperative Oncology Group performance status (ECOG PS), and non-responsiveness to bortezomib.

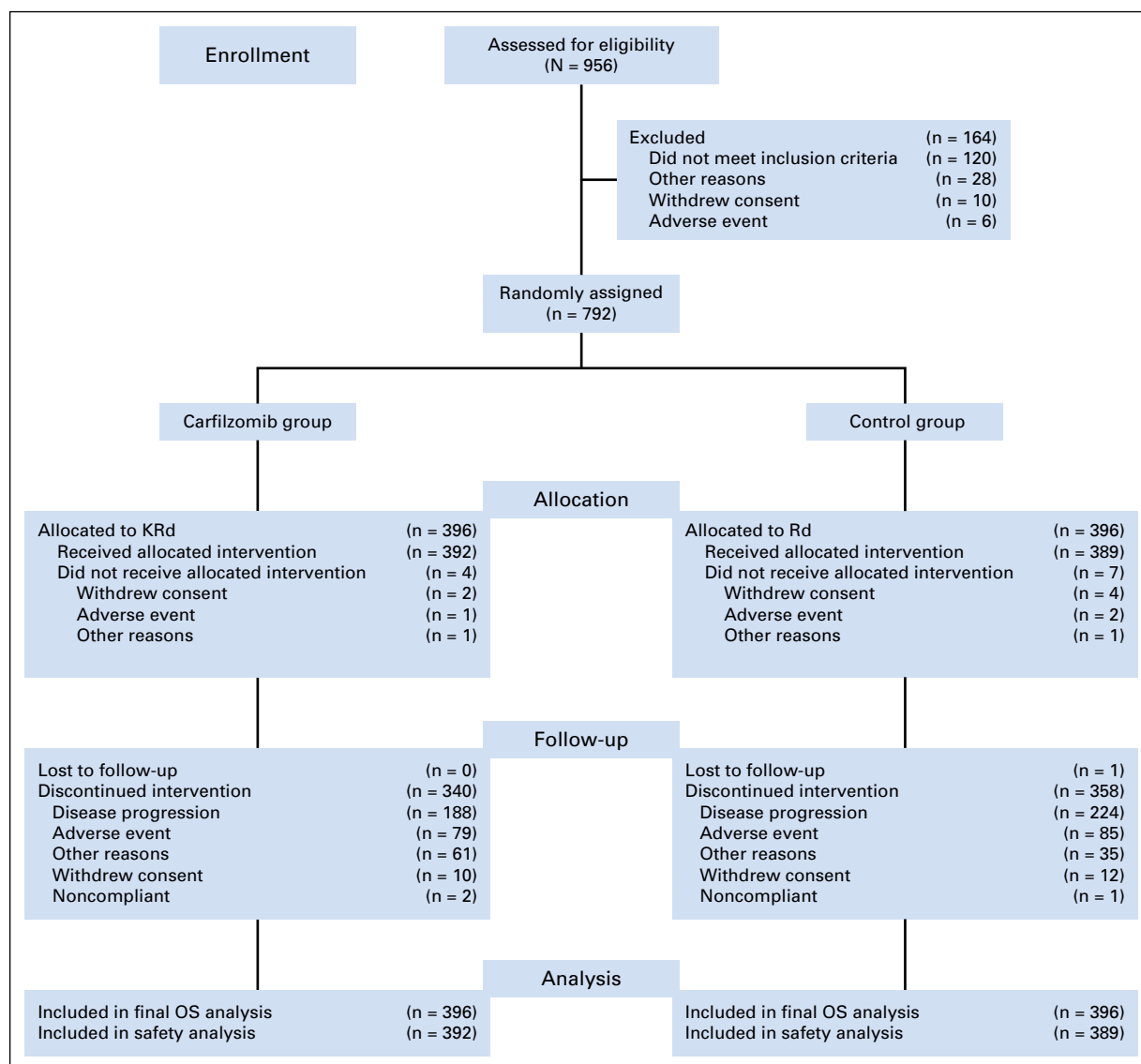
## RESULTS

### Patients

Between July 2010 and March 2012, 792 patients were enrolled in ASPIRE and randomly assigned to KRd (n = 396) or Rd (n = 396; Fig 1). Baseline characteristics were well balanced between treatment groups.<sup>7</sup>

### OS

The cutoff date for the final OS analysis was April 28, 2017. Median follow-up for OS was 67.1 months. At data cutoff, 129 patients receiving KRd (32.6%) and 98 receiving Rd (24.7%) were alive. On the basis of the number of deaths observed, the O'Brien-Fleming stopping boundary for OS benefit (one-sided  $P$  value) was .023.



**Fig 1.** Trial profile. KRd, carfilzomib, lenalidomide, and dexamethasone; OS, overall survival; Rd, lenalidomide and dexamethasone.

Median OS was 48.3 months (95% CI, 42.4 to 52.8 months) in the KRd group and 40.4 months (95% CI, 33.6 to 44.4 months) in the Rd group, representing a 7.9-month prolongation of OS with KRd (HR, 0.79; 95% CI, 0.67 to 0.95; one-sided  $P = .0045$ ; Fig 2). This result crossed the prespecified stopping boundary (one-sided  $P = .023$ ) and was thus statistically significant. Using a piecewise Cox model (Appendix), the 18-month OS HR was estimated as 0.69 (95% CI, 0.51 to 0.93).

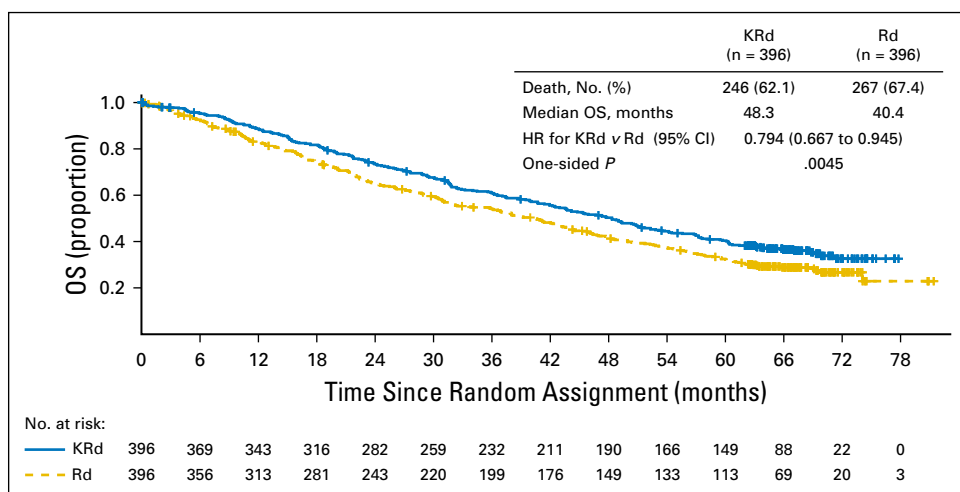
Because OS was statistically significant at the final analysis, the test results for ORR (KRd, 87.1% v Rd, 66.7%; two-sided  $P < .001$ ) and HRQoL (overall treatment effect, 4.2; 95% CI, 2.1 to 6.4; two-sided  $P < .001$ ) obtained at interim<sup>7,12</sup> were statistically significant.

### Subgroup Analyses of OS

Median OS was 11.4 months longer for KRd ( $n = 184$ ) versus Rd ( $n = 157$ ) in patients who had received one prior line of therapy (47.3 v 35.9 months; HR, 0.81; 95% CI, 0.62 to 1.06) and

6.5 months longer for patients (KRd,  $n = 212$ ; Rd,  $n = 239$ ) who had received  $\geq$  two prior lines of therapy (48.8 v 42.3 months; HR, 0.79; 95% CI, 0.62 to 0.99). Among patients who had received one prior line, median OS was improved by 12 months with KRd versus Rd in those with prior bortezomib exposure (KRd,  $n = 93$ ; Rd,  $n = 73$ ; 45.9 v 33.9 months; HR, 0.82; 95% CI, 0.56 to 1.19) and by 7.9 months in those without prior bortezomib (KRd,  $n = 91$ ; Rd,  $n = 84$ ; 48.3 v 40.4 months; HR, 0.80; 95% CI, 0.55 to 1.17). Median OS was also improved by 18.6 months with KRd ( $n = 88$ ) versus Rd ( $n = 78$ ) among patients with prior transplantation at first relapse (57.2 v 38.6 months; HR, 0.71; 95% CI, 0.48 to 1.05).

For patients with R-ISS stage I (KRd,  $n = 42$ ; Rd,  $n = 46$ ), median OS was not reached in the KRd group and was 58.0 months in the Rd group (HR, 0.49; 95% CI, 0.26 to 0.92). For R-ISS stage II (KRd,  $n = 194$ ; Rd,  $n = 195$ ), median OS was 45.4 and 41.2 months in the KRd and Rd groups, respectively (HR, 0.86; 95% CI, 0.68 to 1.10). For patients with R-ISS stage III (KRd,  $n = 37$ ; Rd,  $n = 47$ ), median OS was 23.3 months in the KRd group and 18.8 months in



**Fig 2.** Overall survival (OS): Medians were estimated using the Kaplan-Meier method. Hazard ratio (HR) and P value were obtained from stratified Cox regression and stratified log-rank test, respectively. KRd, carfilzomib, lenalidomide, and dexamethasone; Rd, lenalidomide and dexamethasone.

the Rd group (HR, 1.05; 95% CI, 0.66 to 1.68). Cytogenetic risk status was determined in 53% of patients. OS was improved with KRd versus Rd in standard-risk patients (median, 49.0 v 41.4 months; HR, 0.74; 95% CI, 0.56 to 0.97) and was similar between groups for high-risk patients (KRd, n = 48; Rd, n = 52; median, 36.0 months in each group; HR, 1.08; 95% CI, 0.67 to 1.74). Notably, fewer patients with high-risk cytogenetics in the KRd group received subsequent therapy versus those in the Rd group (39.6% v 57.7%; Appendix Table A1, online only). In contrast, in standard-risk patients (KRd, n = 147; Rd, n = 170), use of subsequent therapies was similar (KRd, 38.1%; Rd, 42.9%).

OS was also improved with KRd versus Rd across subgroups according to age (< 75 years [KRd, n = 353; Rd, n = 343]: HR, 0.80; 95% CI, 0.66 to 0.96; ≥ 75 years [KRd, n = 43; Rd, n = 53]: HR, 0.80; 95% CI, 0.50 to 1.30), ECOG PS (0 or 1 [KRd, n = 356; Rd, n = 361]: HR, 0.79; 95% CI, 0.66 to 0.96; 2 [KRd, n = 40; Rd, n = 35]: HR, 0.69; 95% CI, 0.42 to 1.13), CrCL (30 to < 60 mL/min [KRd, n = 79; Rd, n = 82]: HR, 0.72; 95% CI, 0.51 to 1.02; ≥ 60 mL/min [KRd, n = 316; Rd, n = 308]: HR, 0.81, 95% CI, 0.66 to 0.99), and nonresponsive to bortezomib (KRd, n = 60; Rd, n = 58; HR, 0.73; 95% CI, 0.47 to 1.13).

**Subsequent Antimyeloma Therapy**

After discontinuation from study drug, 284 patients in the KRd group and 304 in the Rd group entered long-term follow-up; 182 patients in the KRd group and 211 in the Rd group received subsequent antimyeloma therapy (Table 1). Subsequent antimyeloma therapies were generally balanced across treatment groups. In post hoc analysis, survival beyond progression was similar between treatment groups (HR, 1.015; 95% CI, 0.81 to 1.27; Appendix Fig A1, online only).

Median time to next treatment (from time of random assignment) was 39.0 months (95% CI, 31.8 to 55.1 months) for patients who received KRd and 24.4 months (95% CI, 20.8 to 28.4 months) for patients who received Rd (HR, 0.65; 95% CI, 0.53 to 0.79; one-sided P < .001).

**Updated Investigator-Assessed PFS**

An updated analysis of investigator-assessed PFS was conducted (data cutoff, April 28, 2017) with longer follow-up (median, 48.8 [KRd] and 48.0 months [Rd]) than previously reported. Median PFS was 26.1 months (95% CI, 23.2 to 30.3 months) in the KRd group

versus 16.6 months (95% CI, 14.5 to 19.4 months) in the Rd group (HR, 0.66; 95% CI, 0.55 to 0.78; one-sided P < .001; Fig 3). Three-year PFS rates were 38.2% (KRd) versus 28.4% (Rd), and 5-year rates were 25.6% (KRd) versus 17.3% (Rd).

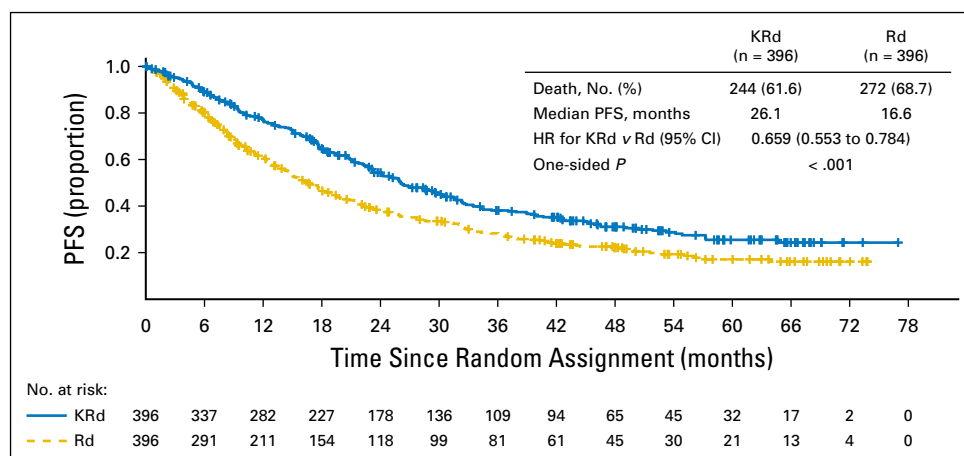
**Safety**

Included in the safety analyses were 392 patients in the KRd group and 389 in the Rd group who received ≥ one dose of study treatment. Median treatment duration of carfilzomib in the KRd group was 72 weeks; median relative dose-intensity of carfilzomib was 93.7%. For the KRd and Rd groups, median treatment duration of lenalidomide was 85 and 57 weeks, respectively. Median treatment duration of dexamethasone was 80 and

**Table 1.** Subsequent Antimyeloma Therapies

Therapy	KRd (n = 396)	Rd (n = 396)
Patients treated with ≥ one therapy	182 (46.0)	211 (53.3)
Systemic corticosteroids		
Dexamethasone	121 (30.6)	129 (32.6)
Prednisone	8 (2.0)	11 (2.8)
Proteasome inhibitors		
Bortezomib	67 (16.9)	105 (26.5)
Carfilzomib	10 (2.5)	8 (2.0)
Immunomodulatory drugs		
Lenalidomide	21 (5.3)	22 (5.6)
Pomalidomide	16 (4.0)	15 (3.8)
Thalidomide	16 (4.0)	10 (2.5)
Antineoplastic agents		
Cyclophosphamide	54 (13.6)	68 (17.2)
Doxorubicin	17 (4.3)	15 (3.8)
Melphalan	16 (4.0)	16 (4.0)
Bendamustine	14 (3.5)	11 (2.8)
Cisplatin	8 (2.0)	7 (1.8)
Blood substitutes and perfusion solutions		
Blood and related products	9 (2.3)	8 (2.0)
Other therapeutic products		
Investigational drug	10 (2.5)	11 (2.8)

NOTE. Values are No. (%). Therapy administered to ≥ 2% of patients in either group. Abbreviations: KRd, carfilzomib, lenalidomide, and dexamethasone; Rd, lenalidomide and dexamethasone.



**Fig 3.** Progression-free survival (PFS) as assessed by investigators. Medians were estimated using the Kaplan-Meier method. Hazard ratio (HR) and *P* value were obtained from Cox regression and log-rank test, respectively. KRd, carfilzomib, lenalidomide, and dexamethasone; Rd, lenalidomide and dexamethasone.

49 weeks, respectively. A total of 85.9% (KRd) and 90.4% (Rd) of randomly assigned patients discontinued treatment, most commonly because of disease progression (47.5% and 56.6%, respectively) or AEs (19.9% and 21.5%, respectively).

Any-grade TEAE rates were 98.0% (KRd) and 97.9% (Rd). The most common AEs are listed in Table 2. The AEs (preferred terms) with frequencies  $\geq 10\%$  higher for KRd versus Rd were cough (29.6% v 18.0%, respectively) and hypokalemia (29.6% v 14.9%, respectively).

Grade  $\geq 3$  TEAE rates were 87.0% (KRd) and 83.3% (Rd), and serious AE rates were 65.3% (KRd) and 56.8% (Rd). Selected

grade  $\geq 3$  AEs of interest (grouped terms; KRd v Rd) included acute renal failure (3.8% v 3.3%), cardiac failure (4.3% v 2.1%), ischemic heart disease (3.8% v 2.3%), hypertension (6.4% v 2.3%), and hematopoietic thrombocytopenia (20.2% v 14.9%). Rates of peripheral neuropathy (grouped term) were similar between groups (any grade, 18.9% v 17.2%, respectively). Fatal TEAEs were reported in 45 patients in the KRd group (11.5%) and 42 patients in the Rd group (10.8%). Fatal TEAEs reported for  $\geq 2$  patients in the KRd group included pneumonia (KRd, n = 6 [1.5%]; Rd, n = 3 [0.8%]), sepsis (KRd, n = 3 [0.8%]; Rd, n = 3 [0.8%]), myocardial

**Table 2.** TEAEs in the Safety Population

TEAE	KRd (n = 392)		Rd (n = 389)	
	All Grades	Grade $\geq 3$	All Grades	Grade $\geq 3$
<b>Most common events*</b>				
Anemia	169 (43.1)	73 (18.6)	158 (40.6)	68 (17.5)
Neutropenia	157 (40.1)	122 (31.1)	136 (35.0)	107 (27.5)
Thrombocytopenia	115 (29.3)	66 (16.8)	94 (24.2)	51 (13.1)
Diarrhea	174 (44.4)	18 (4.6)	145 (37.3)	17 (4.4)
Fatigue	131 (33.4)	32 (8.2)	124 (31.9)	26 (6.7)
Cough	116 (29.6)	1 (0.3)	70 (18.0)	0
Pyrexia	117 (29.8)	7 (1.8)	84 (21.6)	3 (0.8)
Upper respiratory tract infection	118 (30.1)	9 (2.3)	81 (20.8)	4 (1.0)
Hypokalemia	116 (29.6)	41 (10.5)	58 (14.9)	23 (5.9)
Muscle spasms	106 (27.0)	5 (1.3)	82 (21.1)	4 (1.0)
Pneumonia	91 (23.2)	63 (16.1)	66 (17.0)	47 (12.1)
Viral upper respiratory tract infection	80 (20.4)	1 (0.3)	68 (17.5)	0
Nausea	82 (20.9)	3 (0.8)	56 (14.4)	4 (1.0)
Bronchitis	79 (20.2)	8 (2.0)	59 (15.2)	12 (3.1)
Constipation	81 (20.7)	1 (0.3)	70 (18.0)	2 (0.5)
Insomnia	81 (20.7)	12 (3.1)	65 (16.7)	11 (2.8)
Back pain	73 (18.6)	6 (1.5)	83 (21.3)	12 (3.1)
<b>Events of interest†</b>				
Acute renal failure	36 (9.2)	15 (3.8)	30 (7.7)	13 (3.3)
Cardiac failure	28 (7.1)	17 (4.3)	16 (4.1)	8 (2.1)
Ischemic heart disease	27 (6.9)	15 (3.8)	18 (4.6)	9 (2.3)
Hypertension	67 (17.1)	25 (6.4)	34 (8.7)	9 (2.3)
Hematopoietic thrombocytopenia	128 (32.7)	79 (20.2)	102 (26.2)	58 (14.9)
Peripheral neuropathy	74 (18.9)	11 (2.8)	67 (17.2)	12 (3.1)

NOTE. Values are No. (%).

Abbreviations: KRd, carfilzomib, lenalidomide, and dexamethasone; Rd, lenalidomide and dexamethasone; TEAE, treatment-emergent adverse event.

\*AEs (preferred terms) reported in  $\geq 20\%$  of patients in either treatment group.

†Standardized MedDRA query; narrow scope.

infarction (KRd,  $n = 3$  [0.8%]; Rd,  $n = 2$  [0.5%]), acute respiratory distress syndrome (KRd,  $n = 3$  [0.8%]; Rd,  $n = 0$ ), death (KRd,  $n = 2$  [0.5%]; Rd,  $n = 2$  [0.5%]), and cardiac arrest (KRd,  $n = 2$  [0.5%]; Rd,  $n = 1$  [0.3%]). Fatal cardiac disorder rates were 2.6% (KRd) and 2.3% (Rd; Appendix Table A2, online only). No new safety signals were observed for KRd.

AEs were adjusted for person-years of exposure to KRd or Rd. Exposure-adjusted patient incidences of all-grade AEs, grade  $\geq 3$  AEs, serious AEs, and fatal AEs were similar between groups (Appendix Table A3, online only).

## DISCUSSION

Results of the final OS analysis of ASPIRE demonstrate that KRd for 18 cycles led to improved OS in patients with RRMM, with a statistically significant and clinically meaningful 21% decrease in all-cause mortality. Patients treated with KRd had an increase in median OS of 7.9 months over Rd (KRd, 48.3 months; Rd, 40.4 months; HR, 0.79;  $P = .0045$ ). Notably, the OS benefit observed in ASPIRE was not a result of poor outcomes in the Rd group; the reported median OS of 40.4 months in the Rd group is similar to that observed in other phase III studies of RRMM (38.0 to 39.6 months).<sup>18,19</sup>

For patient subgroups by prior lines of therapy, prior bortezomib exposure at first relapse, and prior transplantation at first relapse, there was an 18% to 29% reduction in the risk of death for KRd versus Rd, consistent with findings in the overall population. Notably, there was an 11-month improvement in median OS for patients at first relapse. This OS analysis supports the early use of carfilzomib as effective therapy at first relapse, regardless of prior bortezomib or transplantation exposure. Early treatment with an effective regimen is important to maximize OS, because shorter response durations and increased treatment resistance are associated with each subsequent line of therapy.<sup>20,21</sup>

OS was improved by 8 months with KRd versus Rd among patients with standard-risk cytogenetics. However, an OS benefit for the small number of patients with documented high-risk cytogenetics (KRd,  $n = 48$ ; Rd,  $n = 52$ ) was not observed. Previous analyses showed that PFS was improved in patients treated with KRd, regardless of cytogenetic risk status (standard risk: median, 29.6 v 19.5 months; HR, 0.66; high risk: median, 23.1 v 13.9 months; HR, 0.70).<sup>8</sup> For the high-risk cytogenetic subgroup, the imbalance in use of subsequent antimyeloma treatment may have been a confounding factor, because fewer patients in the KRd group received subsequent antimyeloma therapy. This may have been a result of the limited salvage treatment options available for high-risk patients relapsing with triplet therapy. Additional analyses are warranted to better understand these findings.

Across all age, CrCL, and ECOG PS subgroups, OS HRs favored KRd versus Rd, including in elderly patients (age  $\geq 75$  years), patients with impaired renal function (CrCL 30 to  $< 60$  mL/min), and patients with reduced physical functioning (ECOG PS, 2). Because of small sample sizes in some subgroups, 95% CIs for HRs crossed unity.

Safety results from the final OS analysis were consistent with those previously described in the interim analysis of ASPIRE and with the known safety profile of carfilzomib, with no new safety signals observed after extended follow-up. Although incidences of grade  $\geq 3$  AEs (87.0% v 83.3%) and serious AEs (65.3% v 56.8%) were higher with KRd versus Rd, exposure-adjusted AE rates were

similar between arms, and KRd continued to have a favorable benefit-risk profile. Cardiac AE rates were higher with KRd; however, proactive monitoring and treatment may help resolve these issues.<sup>22,23</sup> Despite prolonged treatment exposure in the KRd versus Rd group, rates of treatment discontinuation because of AEs and fatal AEs were similar in the two groups.

ASPIRE is the second phase III trial in patients with RRMM to demonstrate a statistically significant OS advantage for a carfilzomib-based therapy against a standard of care. The first phase III study was ENDEAVOR, a head-to-head comparison of two proteasome inhibitors (carfilzomib v bortezomib). This study demonstrated that patients who received carfilzomib and dexamethasone had a statistically significant and clinically meaningful OS improvement versus those who received Vd (median, 47.6 v 40.0 months; HR, 0.79; 95% CI, 0.65 to 0.96; one-sided  $P = .010$ ). Taken together, the OS results from ASPIRE and ENDEAVOR support the importance of proteasome inhibition with carfilzomib for RRMM. The carfilzomib dosings used for ASPIRE (27 mg/m<sup>2</sup>; 10-minute infusion) and ENDEAVOR (56 mg/m<sup>2</sup>; 30-minute infusion) were optimized for each treatment regimen<sup>24</sup> and represent the currently approved carfilzomib doses for these regimens.

Studies evaluating other modern therapies are ongoing, with OS data not yet mature. Extended 3-year follow-up data from ELOQUENT-2 showed a trend for improved OS for elotuzumab, lenalidomide, and dexamethasone versus Rd (median, 43.7 v 39.6 months; HR, 0.77; 95% CI, 0.61 to 0.97;  $P = .0257$ ); however, these results did not meet statistical significance.<sup>19</sup> OS results from other phase III studies in relapsed MM, such as TOURMALINE-MM1 (ixazomib plus Rd v Rd),<sup>25</sup> CASTOR (daratumumab plus Vd v Vd),<sup>26</sup> and POLLUX (daratumumab plus Rd v Rd),<sup>27</sup> will also provide information regarding the clinical benefit of modern therapies.

In conclusion, treatment with KRd demonstrated a statistically significant and clinically meaningful 21% reduction in the risk of death versus Rd, with an absolute median OS benefit of 7.9 months. Of note, KRd is a highly effective therapy for patients at first relapse, which should be reflected in future treatment algorithms. No new safety signals emerged. Overall, KRd should be considered a preferred treatment option in RRMM.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at [jco.org](http://jco.org).

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

## Improvement in Overall Survival With Carfilzomib, Lenalidomide, and Dexamethasone in Patients With Relapsed or Refractory Multiple Myeloma

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## Appendix

### Select Eligibility Criteria

Patients previously treated with bortezomib were eligible if they did not experience disease progression during therapy. Patients previously treated with lenalidomide were eligible provided they did not discontinue treatment because of adverse effects, experience disease progression during the first 3 months of therapy with Rd, or experience progression at any time during treatment if Rd was their most recent treatment. Per eligibility criteria, patients were required to have creatinine clearance (CrCL) of  $\geq 50$  mL per minute at screening. However, at baseline before receiving study treatment, 25 patients in the KRd arm and 31 patients in the Rd arm had CrCL  $< 50$  mL per minute, with one patient in the Rd arm having CrCL  $< 30$  mL per minute (Stewart, NEJM 2015). In total, there were 79 patients in the KRd arm and 82 patients in the Rd arm (including the patient with CrCL  $< 30$  mL per minute) with CrCL 30 to  $< 60$  mL per minute. Disease nonresponsive to bortezomib indicated that patients had a less-than-minimal response to any bortezomib-containing regimen, experienced disease progression during any bortezomib-containing regimen, or experienced disease progression within 60 days after the completion of any bortezomib-containing regimen. If patients experienced disease progression during any bortezomib-containing regimen, they were eligible for study enrollment if the date of progression occurred after discontinuation of bortezomib.

### Piecewise Cox Model

Because carfilzomib was no longer administered after 18 cycles, the overall proportionality assumption was checked for hazard ratio and found to be valid. However, the overall survival hazard ratio at 18 months was explored using a piecewise Cox model. As expected, the treatment effect for the period when carfilzomib was administered was higher than for the overall study.

**Table A1.** Prior and Subsequent Therapies by Cytogenetic Risk Status

Therapy	High-Risk Cytogenetics		Standard-Risk Cytogenetics	
	KRd (n = 48)	Rd (n = 52)	KRd (n = 147)	Rd (n = 170)
<b>Prior</b>				
No. of regimens				
Median	2.0	2.0	2.0	2.0
Range	1-4	1-3	1-3	1-4
Received bortezomib	39 (81.3)	35 (67.3)	90 (61.2)	105 (61.8)
<b>Subsequent</b>				
Antineoplastic agents	19 (39.6)	30 (57.7)	56 (38.1)	73 (42.9)
Bortezomib	9 (18.8)	17 (32.7)	29 (19.7)	46 (27.1)
Cyclophosphamide	8 (16.7)	14 (26.9)	17 (11.6)	27 (15.9)
Doxorubicin	8 (16.7)	1 (1.9)	3 (2.0)	6 (3.5)

NOTE. Values are No. (%) unless otherwise indicated. The high-risk subgroup consisted of patients with genetic subtype t(4;14) or t(14;16) or with del(17p) in  $\geq 60\%$  of plasma cells as determined by the central laboratories. The standard-risk subgroup consisted of all other patients with known baseline cytogenetic status. Abbreviations: KRd, carfilzomib, lenalidomide, and dexamethasone; Rd, lenalidomide and dexamethasone.

**OS in Patients With RRMM Treated With KRd Versus Rd**

**Table A2.** Fatal Treatment-Emergent Cardiac Disorders (safety population)

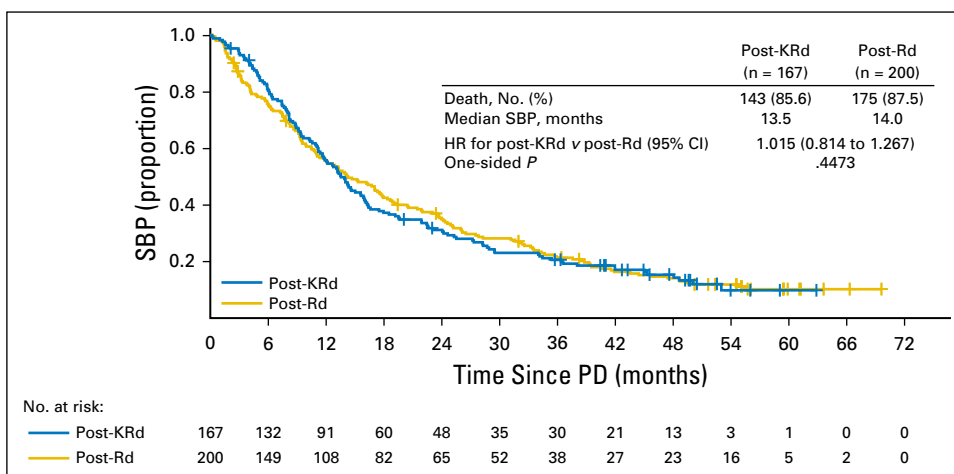
Cardiac Disorder	KRd (n = 392)	Rd (n = 389)
Total	10 (2.6)	9 (2.3)
Myocardial infarction	3 (0.8)	2 (0.5)
Cardiac arrest	2 (0.5)	1 (0.3)
Cardiac failure	1 (0.3)	3 (0.8)
Cardiopulmonary failure	1 (0.3)	1 (0.3)
Acute myocardial infarction	1 (0.3)	0
Cardiac failure acute	1 (0.3)	0
Left ventricular dysfunction	1 (0.3)	0
Acute coronary syndrome	0	1 (0.3)
Arrhythmia	0	1 (0.3)

NOTE. Values are No. (%) unless otherwise indicated.  
Abbreviations: KRd, carfilzomib, lenalidomide, and dexamethasone; Rd, lenalidomide and dexamethasone.

**Table A3.** Exposure-Adjusted AEs (safety population)

AE	r* (95% CI)	
	KRd (n = 392)	Rd (n = 389)
Any grade	588.06 (532.08 to 649.91)	575.53 (520.55 to 636.32)
Grade ≥ 3	115.67 (104.02 to 128.62)	128.27 (115.03 to 143.02)
Serious	48.18 (42.63 to 54.46)	49.48 (43.37 to 56.46)
Grade 5 (fatal)	5.09 (3.80 to 6.82)	6.23 (4.61 to 8.43)

Abbreviations: AE, adverse event; KRd, carfilzomib, lenalidomide, and dexamethasone; Rd, lenalidomide and dexamethasone.  
\*r is the exposure-adjusted patient rate per 100 patient-years (ratio of the total No. of patients with events and total person-time at risk in years multiplied by 100).



**Fig A1.** Survival beyond progression (SBP). Survival curves and median SBP in this plot were derived by the Kaplan-Meier method; other statistics reported in the figure are from an unstratified Cox proportional hazards model. HR, hazard ratio; KRd, carfilzomib, lenalidomide, and dexamethasone; PD, disease progression; Rd, lenalidomide and dexamethasone.