Carfilzomib-Dexamethasone Versus Bortezomib-Dexamethasone in Relapsed or Refractory Multiple Myeloma: Updated Overall Survival, Safety, and Subgroups

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Abstract

In this updated analysis of patients with relapsed/refractory multiple myeloma (RRMM) from the RandomizEd, OpeN Label, Phase 3 Study of Carfilzomib Plus DExamethAsone Vs Bortezomib Plus DexamethasOne in Patients With Relapsed Multiple Myeloma (ENDEAVOR) trial, clinically meaningful overall survival improvements continue to be observed with carfilzomib 56 mg/m^2 and dexamethasone (Kd56; n = 464) versus bortezomib and dexamethasone (n = 465), including in key patient subgroups. With longer-term data, the favorable benefit-risk profile of Kd56 continues to support its use as a standard-of-care in RRMM.

Introduction: The phase III RandomizEd, OpeN Label, Phase 3 Study of Carfilzomib Plus DExamethAsone Vs Bortezomib Plus DexamethasOne in Patients With Relapsed Multiple Myeloma (ENDEAVOR) trial showed significantly improved progression-free survival and overall survival (OS) with carfilzomib (56 mg/m^2) and dexamethasone (Kd56) versus bortezomib and Kd56 (Vd) in patients with relapsed or refractory multiple myeloma (RRMM). We report updated OS and safety data after 6 months of additional follow-up. **Patients and Methods:** Patients with RRMM (1-3 previous lines of therapy) were randomized 1:1 to Kd56 or Vd. Median OS was estimated using the Kaplan–Meier method; OS was compared between treatment groups using Cox proportional hazards models. **Results:** As of July 19, 2017, median follow-up was 44.3 months for Kd56 and 43.7 months for Vd. Median OS was 47.8 months (Kd56) versus 38.8 months (Vd; hazard ratio, 0.76; 95% confidence interval, 0.633-0.915). OS was longer with Kd56 versus Vd within age and cytogenetic subgroups, and according to number of previous lines of therapy, previous bortezomib exposure, previous lenalidomide exposure, and lenalidomide-refractory status. Exposure-adjusted incidences per 100 patient-years of adverse events (AEs) were 1352.07 for Kd56 and 1754.86 for Vd; for Grade ≥3 AEs, these values were 162.31 and 175.90. **Conclusion:** With median follow-up of approximately 44 months, clinically meaningful improvements in OS were observed with Kd56 versus Vd, including in all subgroups examined. The Kd56 safety profile was consistent with previous analyses.

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Introduction

As treatment options for multiple myeloma (MM) increase, treatment paradigms are changing. The use of novel therapies has resulted in improved outcomes; however, patients with MM usually relapse[1] and improving outcomes obtained with subsequent lines of therapy, particularly across the heterogeneous relapsed or refractory MM (RRMM) patient population, remains a challenge. The "gold standard" therapeutic goal for any agent used in oncology is extended overall survival (OS).[2] To date, only 2 MM clinical trials, the RandomizEd, OpeN Label, Phase 3 Study of Carfilzomib Plus DExamethAsone Vs Bortezomib Plus DexamethasOne in Patients With Relapsed Multiple Myeloma (ENDEAVOR) trial and the CArfilzomib, Lenalidomide, and DexamethaSone versus Lenalidomide and Dexamethasone for the treatment of PatIents with Relapsed Multiple MyEloma (ASPIRE) trial, have shown a statistically significant improvement in OS beyond that observed using a recent standard-of-care regimen containing either lenalidomide or the first-generation proteasome inhibitor (PI) bortezomib.[3-5]

At the time of the ENDEAVOR (NCT01568866) study design, standard therapy for MM that included a PI consisted of fixed-duration therapy. Fixed-duration therapy is appropriate when such therapy is curative, or when exposure above a threshold causes toxicity. Because RRMM is incurable, and the dose-limiting toxicity for the comparator arm is sensory neuropathy, it was considered ethical to allow a continuous therapy design. Continuous therapy with carfilzomib (56 mg/m^2) and dexamethasone (Kd56) versus bortezomib and dexamethasone (Vd), with stratification on the basis of previous exposure to PI, was deemed balanced. The study design maximized treatment effect for each agent, allowing a true comparison of efficacy of these 2 PIs. The primary end point of progression-free survival (PFS) and secondary end point of OS were met.[3,4] In a prespecified interim analysis, the median OS was 47.6 months (95% confidence interval [CI], 42.5 to not estimable [NE]) in the Kd56 group versus 40.0 months (95% CI, 32.6-42.3) in the Vd group (hazard ratio [HR], 0.791; 95% CI, 0.648-0.964; 1-sided $P = .010$).[3]

Figure 1 Trial Profile

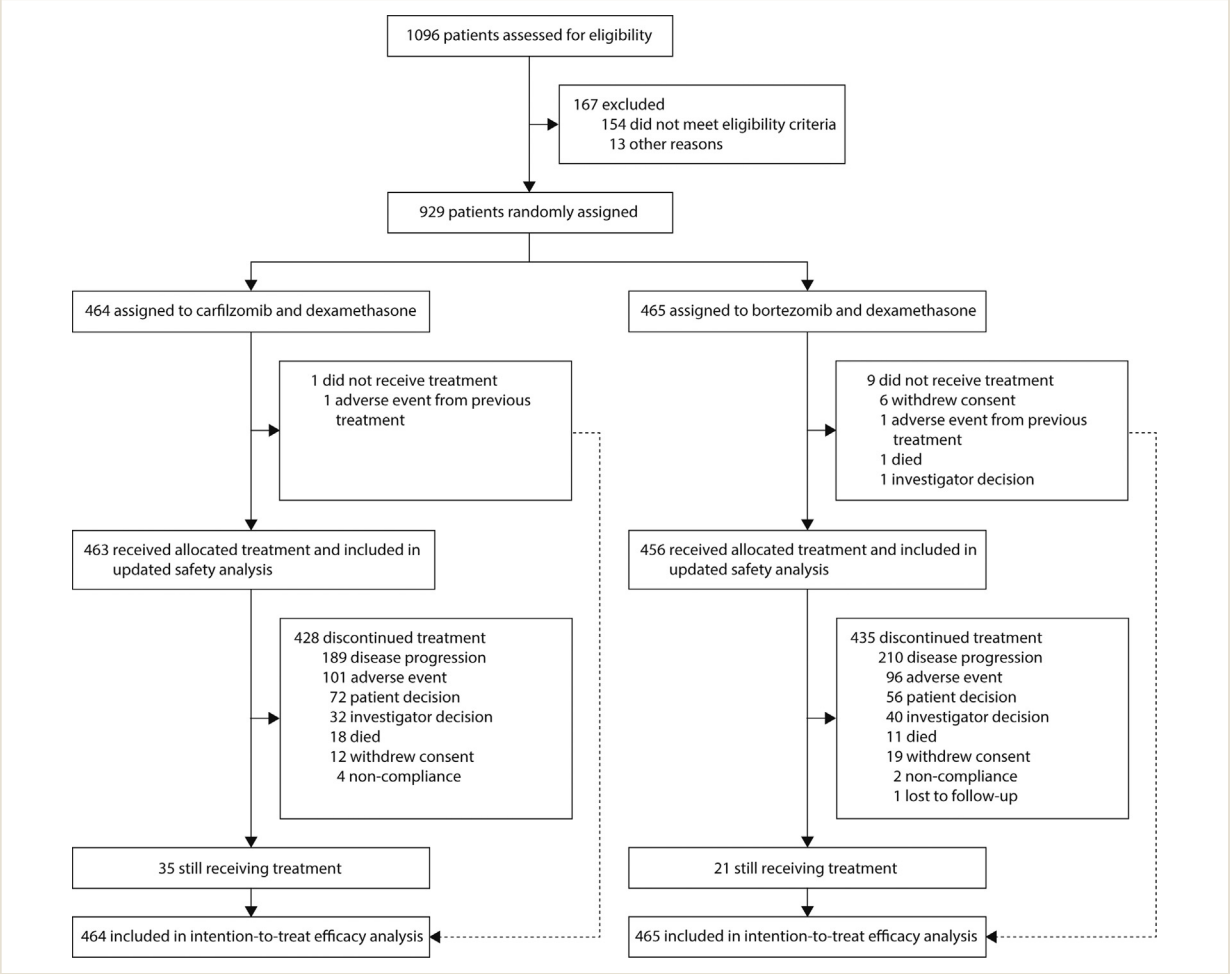
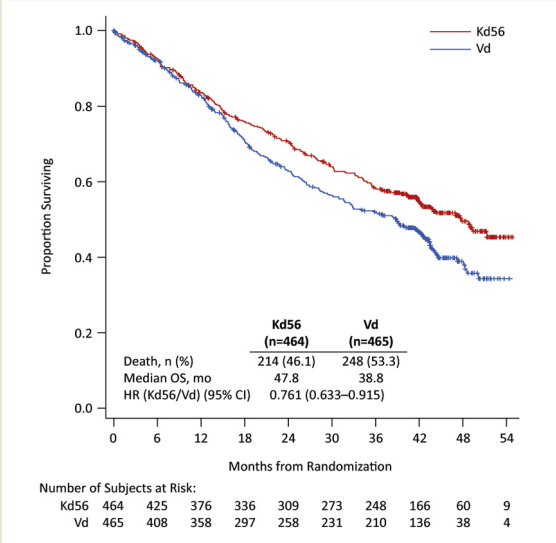


Figure 2 Kaplan–Meier Curve of Overall Survival (Intent-to-Treat Population). The Curve Was Truncated at the Time Point When Only 10 Subjects (Kd56 and Vd Combined) Were at Risk



Abbreviations: HR = hazard ratio; Kd56 = carfilzomib (56 mg/m^2) and dexamethasone; OS = overall survival; Vd = bortezomib and dexamethasone.

The ENDEAVOR study remained open to fulfill a postmarketing requirement that the sponsor submits a report of safety and efficacy outcomes with at least 3 years of follow-up data on long-term treatment. In July 2017, all ENDEAVOR patients had received 3 years of follow-up. Herein we report updated exposure and survival data from the 3-year data cutoff.

Patients and Methods

Study Design and Patients

The ENDEAVOR trial design has been described previously.[3,4] Briefly, ENDEAVOR was a phase III, randomized, open-label study of adult patients with RRMM who had received 1 to 3 previous lines of therapy.

Patients were randomized 1:1 to receive Kd56 or Vd. Randomization was stratified in accordance with several baseline factors: International Staging System stage (I vs. II-III); lines of previous treatment (1 vs. 2 or 3 lines); previous PI treatment (previous vs. no previous carfilzomib or bortezomib treatment); and planned route of bortezomib administration (intravenous [IV] vs. subcutaneous).

In the Kd56 group, patients received carfilzomib as an IV infusion over 30 minutes on days 1, 2, 8, 9, 15, and 16 of 28-day cycles. The carfilzomib dose was 20 mg/m^2 on days 1 and 2 of cycle 1, followed by 56 mg/m^2 thereafter. Dexamethasone 20 mg was administered orally or IV on days 1, 2, 8, 9, 15, 16, 22, and 23. Patients in the Vd group received bortezomib 1.3 mg/m^2 as an IV bolus or subcutaneous injection on days 1, 4, 8, and 11 of each 21-day cycle. Dexamethasone (20 mg; oral or IV) was administered on days 1, 2, 4, 5, 8, 9, 11, and 12. Treatment was given until disease progression, physician decision, unacceptable toxicity, withdrawal of consent, or death. Safety follow-up continued for all patients receiving treatment and through 30 days after treatment discontinuation.

The institutional review board/ethics committee at each participating site approved the study, and the protocol conformed to Good Clinical Practice Guidelines and the principles of the Declaration of Helsinki. All participants provided written informed consent.

Data Sharing

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

Assessments

Cytogenetic analyses were carried out using fluorescence in situ hybridization (FISH) to determine the risk status of patients. Those defined as being at "high risk" were patients with the genetic subtypes t(4;14) or t(14;16) in ≥10% of screened plasma cells, or with del(17p) in ≥20% of screened plasma cells. All other patients with available and known baseline cytogenetics were included in the "standard risk" subgroup. Patients with a FISH assessment whose data could not be analyzed or did not yield a definitive result were included in the "unknown/missing" cytogenetics subgroup.[6]

The severity of adverse events (AEs) was classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03, and AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0. For selected AEs of interest (acute renal failure, cardiac failure, peripheral neuropathy, ischemic heart disease, and hematopoietic thrombocytopenia), standardized MedDRA query narrow scope (SMQN) grouped terms were applied. Patients who discontinued treatment before disease progression were followed-up every 4 weeks for disease status until progression. After disease progression, patients were followed for survival status every 3 months.

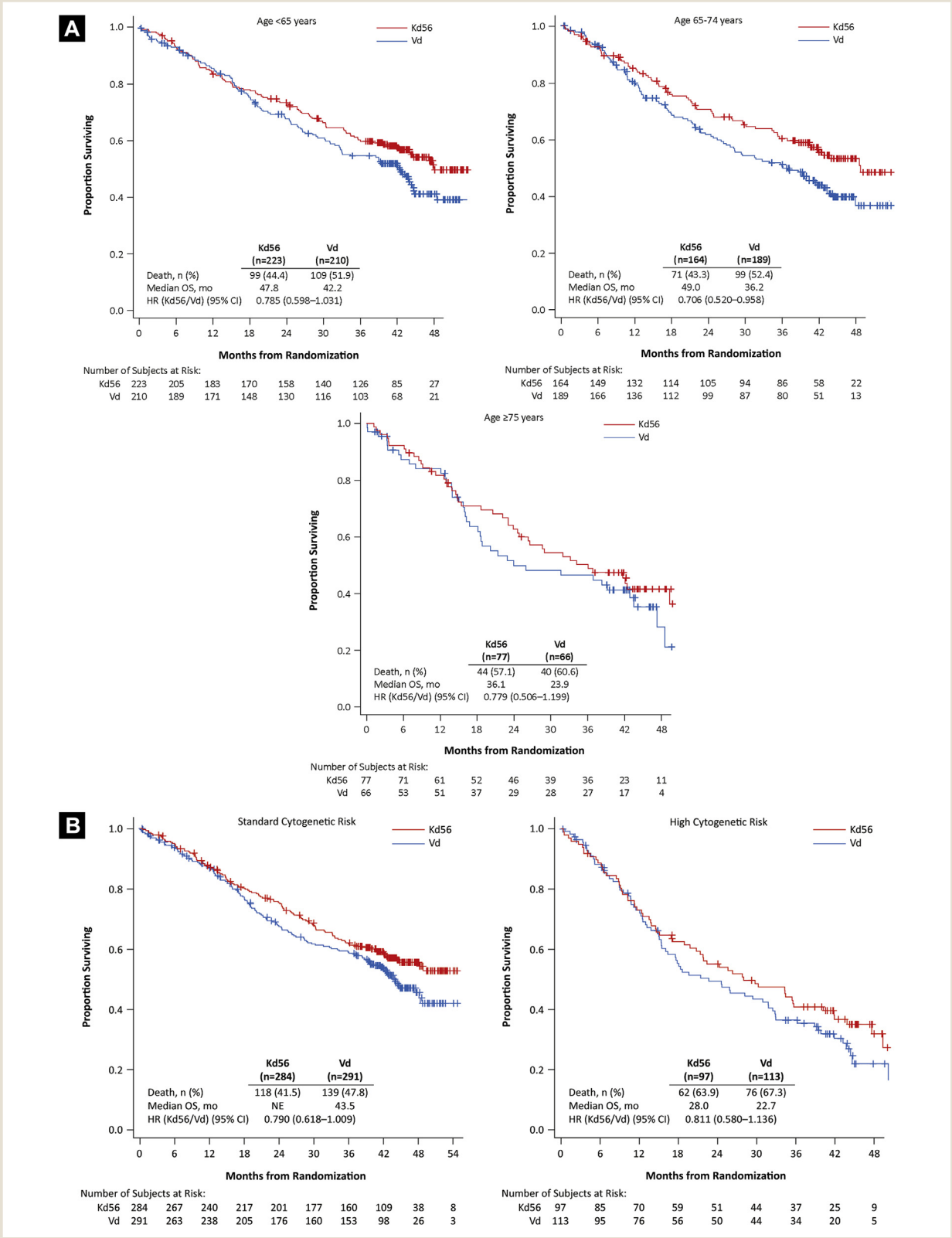
Outcomes

The primary end point of ENDEAVOR was PFS. Secondary end points were OS, overall response rate, duration of response, incidence of Grade ≥2 peripheral neuropathy, and safety. The final PFS, overall response, and duration of response results were reported in the first interim analysis of ENDEAVOR (data cutoff November 10, 2014).[4] Subsequently, final OS data were reported from a prospectively planned interim OS analysis (data cutoff January 3, 2017).[3] Herein we report updated OS and safety data using a more recent data cutoff of July 19, 2017, including OS data from subgroup analyses. Subgroups included patient age, cytogenetic risk group, previous therapy received, and number of lines of previous treatment.

Statistical Analysis

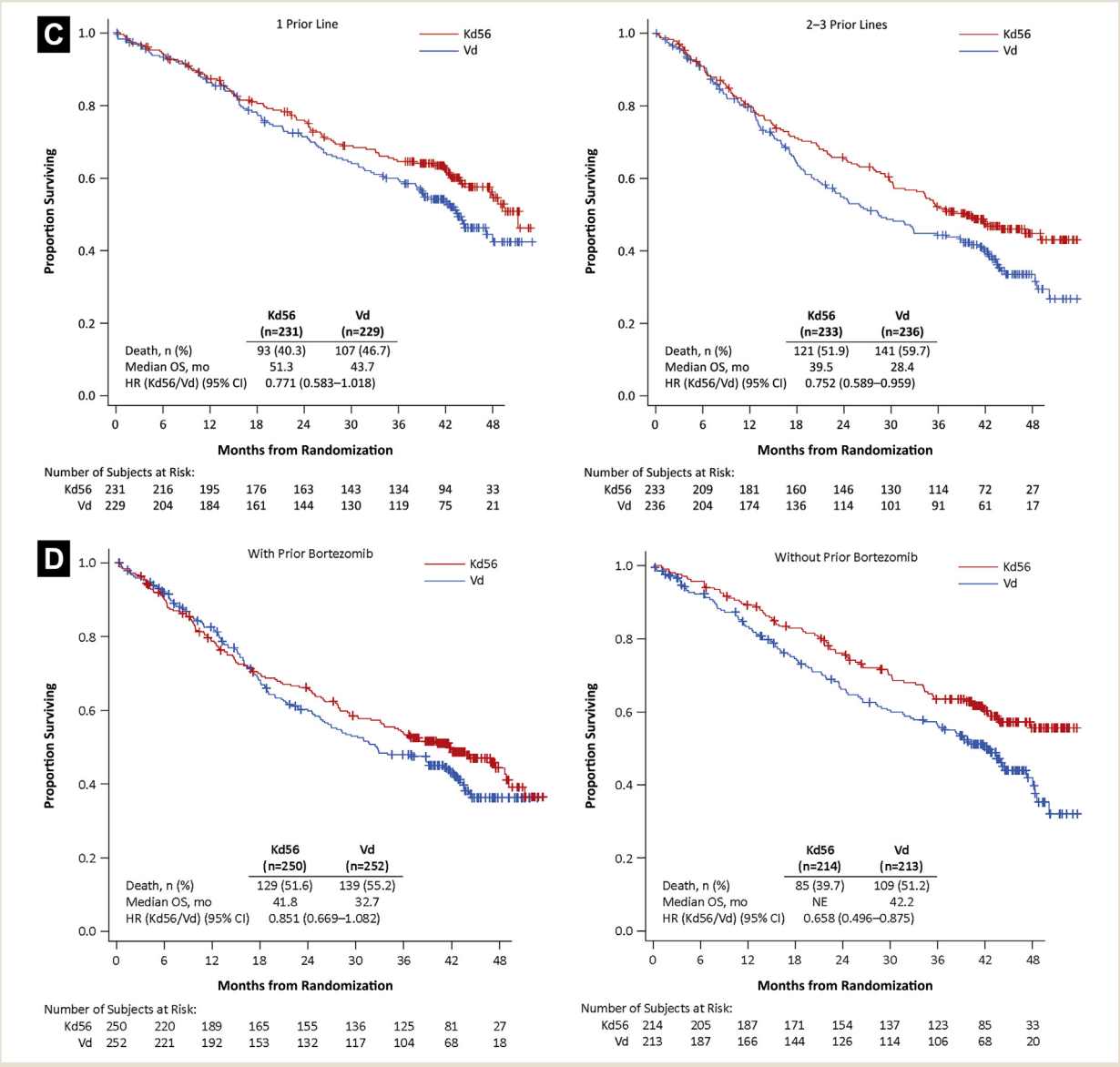
Median OS was estimated using the Kaplan–Meier method. CIs for the median were estimated using the method by Klein and Moeschberger with log-log transformation.[7] For the comparison of OS between treatment groups, HRs and corresponding 95% CIs were estimated using stratified or unstratified Cox proportional hazards models for the primary intent-to-treat (ITT) population and

Figure 3 Kaplan–Meier Curves of Overall Survival (OS) According to Subgroup. (A) Age; (B) Cytogenetic Risk; (C) Number of Previous Lines of Therapy; (D) Previous Bortezomib Treatment; and (E) Previous Lenalidomide Treatment. The Curves Were Truncated at the Time Point When Only 10 Subjects (Kd56 and Vd Combined) Were at Risk



Abbreviations: HR = hazard ratio; Kd56 = carfilzomib (56 mg/m^2) and dexamethasone; NE = not estimable; Vd = bortezomib and dexamethasone.

Figure 3 continued



subgroup OS analyses, respectively. Exposure-adjusted patient incidences per 100 patient-years were calculated. Total person-time in each treatment group was the sum of the time to first treatment-emergent AE for each patient, or the entire time of exposure to study drug if a patient had no event.

Results

Patients

Between June 20, 2012, and June 30, 2014, 929 eligible patients were enrolled in ENDEAVOR and randomly assigned to the Kd56 group (n = 464) or the Vd group (n = 465; Figure 1).

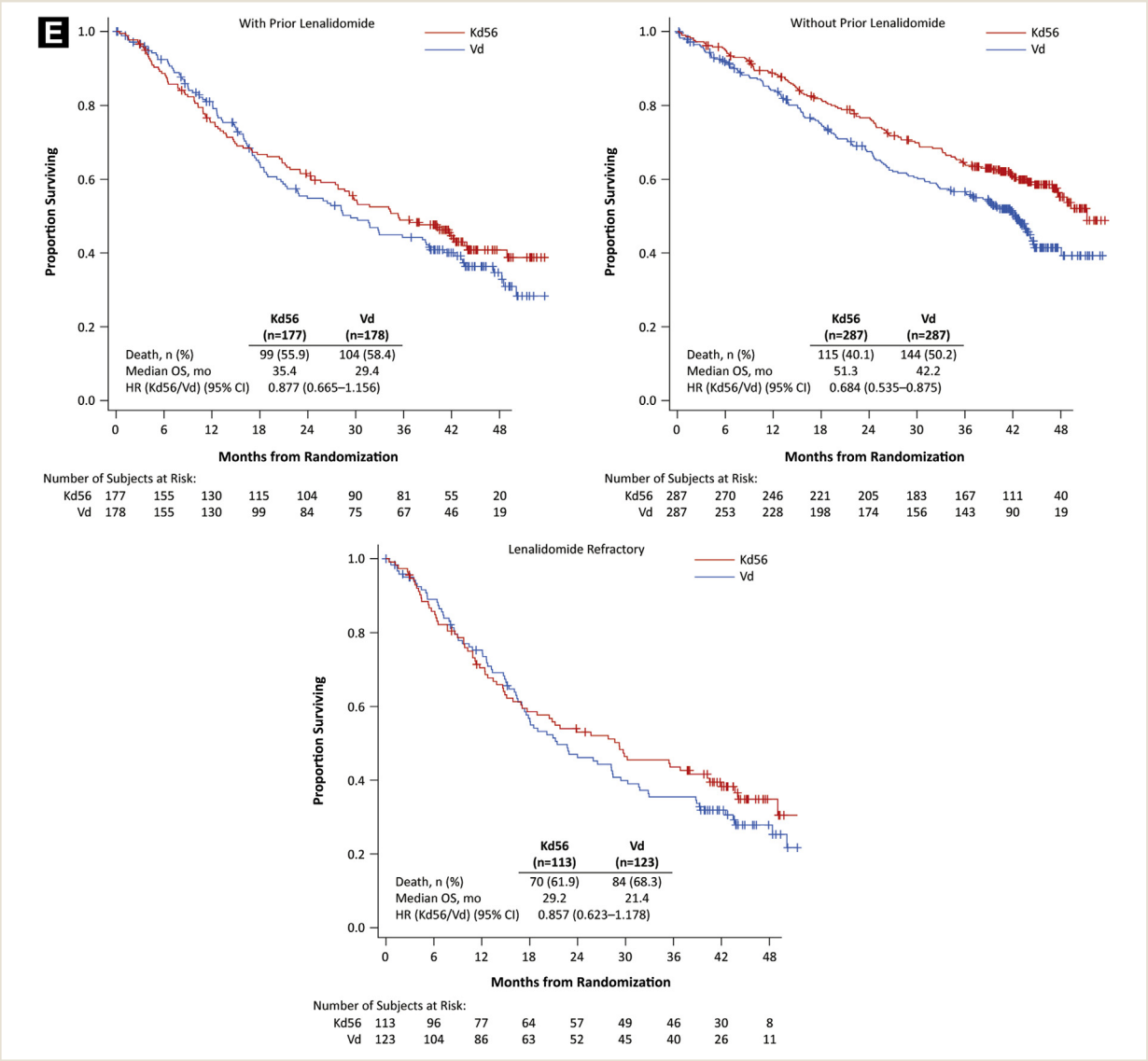
Overall Survival

The number of patients alive at the cutoff on July 19, 2017, was 214 (46.1%) in the Kd56 group and 168 (36.1%) in the Vd group. Median follow-up time for OS was 44.3 months in the Kd56 group and 43.7 months in the Vd group. The median OS for the ITT population was 9.0 months longer in the Kd56 group (median, 47.8 months; 95% CI, 41.9-NE) versus the Vd group (median, 38.8 months; 95% CI, 31.7-42.7), resulting in an HR of 0.76 (95% CI, 0.63-0.92; 1-sided $P = .0017$; Figure 2).

Subgroup Analyses of OS

Kaplan–Meier curves of OS according to patient subgroups are shown in Figure 3. Median OS was longer in the Kd56 versus Vd groups, regardless of patient age. In patients aged ≥75 years, median OS was 36.1 versus 23.9 months (HR, 0.78; 95% CI, 0.51-1.20; Kd56, n = 77; Vd, n = 66). For patients aged 65 to 74 years, median OS was 49.0 versus 36.2 months (HR, 0.71; 95% CI, 0.52-0.96; Kd56, n = 164; Vd, n = 189), and for those aged <65

Figure 3 continued



years, median OS was 47.8 versus 42.2 months (HR, 0.79; 95% CI, 0.60-1.03; Kd56, n = 223; Vd, n = 210). To assess potential reasons for the greater difference in median OS between treatment arms in the older patient subgroups compared with the <65-year-old subgroup, subsequent salvage regimens were evaluated in each age subgroup. The percentage of patients treated with at least 1 subsequent antimyeloma salvage therapy was similar between Kd56- versus Vd-treated patients in each age subgroup (see Supplemental Table 1 in the online version). The percentage of patients treated with specific antimyeloma salvage therapies, including lenalidomide, cyclophosphamide, and pomalidomide, were also similar between Kd56- versus Vd-treated patients across age subgroups. Bortezomib was the only subsequent antimyeloma therapy that showed a >10% difference between the Kd56 and Vd arms within each age group, but these differences were similar across age groups.

Cytogenetic risk status was evaluated for 381/464 (82%) patients in the Kd56 group and 404/465 (87%) patients in the Vd group. When assessed according to cytogenetic risk status, median OS was longer in the Kd56 group versus the Vd group for high-risk patients (median OS, 28.0 vs. 22.7 months; HR, 0.81; 95% CI, 0.58-1.14; Kd56, n = 97; Vd, n = 113) and standard-risk patients (median OS, NE vs. 43.5 months; HR, 0.79; 95% CI, 0.62-1.01; Kd56, n = 284; Vd, n = 291).

Median OS was longer in the Kd56 group, regardless of the number of lines of previous therapy received. In patients in the Kd56 (n = 231) versus Vd (n = 229) groups who had received 1 previous line of therapy, the median OS was 51.3 versus 43.7 months, respectively (HR, 0.77; 95% CI, 0.58-1.02). Similarly, in patients previously treated with 2 to 3 lines, median OS was 39.5 versus 28.4 months in the Kd56 (n = 233) versus Vd (n = 236) groups, respectively (HR, 0.75; 95% CI, 0.59-0.96).

Table 1 Summary of Adverse Events in the Safety Population

	Kd56 (n = 463)	Vd (n = 456)
Any Adverse Event, n (%)	457 (98.7)	451 (98.9)
Exposure-Adjusted Incidence of Adverse Events, Rate Per 100 Patient-Years (95% CI)	1352.07 (1233.62-1481.89)	1754.86 (1600.15-1924.53)
Any Grade 3 or Higher Adverse Event, n (%)	379 (81.9)	324 (71.1)
Exposure-Adjusted Incidence of Grade 3 or Higher Adverse Events, Rate Per 100 Patient-Years (95% CI)	162.31 (146.77-179.50)	175.90 (157.75-196.13)
Any Serious Adverse Event, n (%)	279 (60.3)	183 (40.1)
Any Adverse Event Leading to Carfilzomib or Bortezomib Dose Reduction, n (%)	138 (29.8)	226 (49.6)
Any Adverse Event Leading to Treatment Discontinuation, n (%)	137 (29.6)	121 (26.5)
Any Adverse Event Leading to Death, n (%)	32 (6.9)	22 (4.8)

Abbreviations: Kd56 = carfilzomib (56 mg/m^2) and dexamethasone; Vd = bortezomib and dexamethasone.

Median OS was longer in the Kd56 group versus the Vd group, regardless of previous exposure to bortezomib. Median OS for the Kd56 group versus the Vd group was 41.8 versus 32.7 months (HR, 0.85; 95% CI, 0.67-1.08) for patients with previous bortezomib exposure (Kd56, n = 250; Vd, n = 252) and NE versus 42.2 months (HR, 0.66; 95% CI, 0.50-0.88) for patients without previous bortezomib exposure (Kd56, n = 214; Vd, n = 213).

Median OS was longer in the Kd56 group compared with the Vd group regardless of previous exposure to lenalidomide. Median OS for the Kd56 group versus the Vd group was 35.4 versus 29.4 months (HR, 0.88; 95% CI, 0.67-1.16) for patients with previous lenalidomide exposure (Kd56, n = 177; Vd, n = 178) and 51.3 versus 42.2 months (HR, 0.68; 95% CI, 0.54-0.88) for those without previous lenalidomide exposure (Kd56, n = 287; Vd, n = 287). Median OS was also longer in the Kd56 group versus the Vd group regardless of whether or not patients were refractory to any previous lenalidomide treatment for MM. Median OS for the Kd56 group versus the Vd group was 29.2 versus 21.4 months (HR, 0.86; 95% CI, 0.62-1.18) for lenalidomide-refractory patients (Kd56, n = 113; Vd, n = 123) and NE versus 42.8 months (HR, 0.74; 95% CI, 0.59-0.93) for those who were not refractory to a previous lenalidomide treatment (Kd56, n = 351; Vd, n = 342).

Safety

Overall, 457 (98.7%) patients in the Kd56 group and 451 (98.9%) patients in the Vd group experienced an AE (Table 1). Exposure-adjusted patient incidence per 100 patient-years of AEs overall were 1352.07 (95% CI, 1233.62-1481.89) for the Kd56 group and 1754.86 (95% CI, 1600.15-1924.53) for the Vd group. Grade ≥3 AEs occurred in 379 (81.9%) patients in the Kd56 group and 324 (71.1%) in the Vd group (exposure-adjusted patient incidence per 100 patient-years were 162.31 [95% CI,

Table 2 Treatment-Emergent Adverse Events in the Safety Population

	Kd56 (n = 463)		Vd (n = 456)	
	All Grades	Grade 3 or Higher	All Grades	Grade 3 or Higher
Most Common Events, n (%)[a]				
Anemia	202 (43.6)	80 (17.3)	130 (28.5)	46 (10.1)
Diarrhea	170 (36.7)	19 (4.1)	185 (40.6)	40 (8.8)
Pyrexia	151 (32.6)	14 (3.0)	70 (15.4)	3 (0.7)
Hypertension	150 (32.4)	69 (14.9)	46 (10.1)	15 (3.3)
Fatigue	149 (32.2)	32 (6.9)	140 (30.7)	35 (7.7)
Dyspnea	149 (32.2)	29 (6.3)	62 (13.6)	10 (2.2)
Events of Interest, n (%)				
Cardiac failure (SMQN)	51 (11.0)	28 (6.0)	16 (3.5)	9 (2.0)
Ischemic heart disease (SMQN)	18 (3.9)	12 (2.6)	9 (2.0)	7 (1.5)
Peripheral neuropathy (SMQN)	97 (21.0)	11 (2.4)	249 (54.6)	44 (9.6)
Acute renal failure (SMQN)	50 (10.8)	27 (5.8)	29 (6.4)	16 (3.5)
Hematopoietic thrombocytopenia (SMQN)	148 (32.0)	58 (12.5)	123 (27.0)	67 (14.7)
Neutropenia (PT)	29 (6.3)	12 (2.6)	26 (5.7)	10 (2.2)

Abbreviations: Kd56 = carfilzomib (56 mg/m^2) and dexamethasone; PT = preferred term; SMQN = standardized Medical Dictionary for Regulatory Activities query, narrow scope; Vd = bortezomib and dexamethasone.
[a]Adverse events (preferred terms) are included if reported in ≥30% of patients in either treatment group.

Table 3 Treatment-Emergent Adverse Events Over Time in the Safety Population

	Month 0 to ≤12		Month 12 to ≤24		Month 24 to ≤36		Month >36	
	Kd56 (n = 463)	Vd (n = 456)	Kd56 (n = 212)	Vd (n = 104)	Kd56 (n = 89)	Vd (n = 41)	Kd56 (n = 50)	Vd (n = 25)
Any Grade 3 or Higher Adverse Event, n (%)	343 (74.1)	306 (67.1)	112 (52.8)	44 (42.3)	42 (47.2)	15 (36.6)	27 (54.0)	7 (28.0)

Abbreviations: Kd56 = carfilzomib (56 mg/m^2) and dexamethasone; Vd = bortezomib and dexamethasone.

146.77-179.50] and 175.90 [95% CI, 157.75-196.13], respectively).

The most commonly occurring AEs and AEs of interest are shown in Table 2. Grade ≥3 cardiac failure (SMQN) occurred in 28 (6.0%) patients in the Kd56 group and 9 (2.0%) in the Vd group. Cardiac failure (SMQN) led to carfilzomib or bortezomib dose reduction in 8 (1.7%) patients in the Kd56 group and no patient in the Vd group. Cardiac failure (SMQN) led to discontinuation of any treatment in 18 (3.9%) patients in the Kd56 group and 4 (0.9%) patients in the Vd group.

Grade 3 hypertension was reported in 69 (14.9%) patients in the Kd56 group and 15 (3.3%) patients in the Vd group. Hypertension led to reduction of carfilzomib dose in 11 (2.4%) patients in the Kd56 group and no patient in the Vd group. No patient in either treatment group discontinued carfilzomib or bortezomib treatment because of hypertension.

Grade ≥2 peripheral neuropathy (SMQN) was reported in 32 (6.9%) patients in the Kd56 group and 159 (34.9%) in the Vd group. Peripheral neuropathy (SMQN) led to carfilzomib dose reduction in 9 (1.9%) patients in the Kd56 group and bortezomib dose reduction in 142 (31.1%) patients in the Vd group. Peripheral neuropathy (SMQN) led to discontinuation of any treatment in 2 (0.4%) patients in the Kd56 group and 40 (8.8%) patients in the Vd group.

Infections and infestations (system organ class) were reported in 368 (79.5%) patients in the Kd56 group and 319 (70.0%) patients in the Vd group. Grade ≥3 AEs in this class were reported in 148 (32.0%) patients and 94 (20.6%) patients, respectively.

The incidence of Grade ≥3 AEs decreased over time in both treatment groups (Table 3). In total, 343 (74.1%) patients of 463 receiving Kd56 experienced a Grade ≥3 AE between 0 to ≤12 months, 112 (n = 212; 52.8%) within 12 to ≤24 months, 42 (n = 89; 47.2%) between 24 to ≤36 months, and 27 (n = 50; 54.0%) beyond 36 months of treatment. A total of 306 (67.1%) of 456 patients receiving Vd reported grade ≥3 AEs from 0 to ≤12 months, 44 (n = 104; 42.3%) between 12 to ≤24 months, 15 (n = 41; 36.6%) between 24 to ≤36 months, and 7 (n = 25; 28.0%) beyond 36 months from Vd start date.

At 36 months, 35 patients (7.5%) in the Kd56 group and 21 patients (4.5%) in the Vd group were still receiving treatment.

Discussion

The phase III ENDEAVOR trial evaluated the efficacy and safety of Kd56 versus Vd in patients with RRMM. The initial publications from ENDEAVOR reported significant improvements in OS (21% reduction in the risk of death), PFS, and responses for patients receiving treatment with Kd56 versus Vd.[3,4] In the present analysis with longer follow-up (median follow-up of approximately 44 months), OS results continued to show improvement with Kd56 versus Vd (median OS, 47.8 vs. 38.8 months; HR, 0.76; 95% CI, 0.63-0.92; 1-sided $P = .0017$).

In the interim OS analysis, treatment with Kd56 also improved OS across several patient subgroups,[3] and this continues with an additional 6 months of follow-up. For patient subgroups according to previous lines of therapy, previous bortezomib exposure, previous lenalidomide exposure, and lenalidomide-refractory status, there was a 12% to 34% reduction in the risk of death for the Kd56 group versus the Vd group. Across all age and cytogenetic subgroups, an OS benefit was shown for Kd56 versus Vd, including in elderly patients (≥75 years) and patients with high-risk cytogenetics.

Late phase clinical trials include measures of clinical benefit that support regulatory approval. Although measurement of OS requires prolonged trials, and OS outcomes might be confounded by the availability of active therapeutics used in later lines, OS remains the oncology end point preferred by the European Medicines Agency, the Food and Drug Administration, and other health authorities for regulatory approval.

The safety data obtained during this analysis were consistent with those previously reported from the first and final analyses of ENDEAVOR.[3,4] The exposure-adjusted incidence per 100 patient-years of AEs was lower in patients treated with Kd56 than Vd (1352.07 vs. 1754.86). Although the number of patients with reported Grade ≥3 AEs was higher with carfilzomib than with bortezomib (379 [81.9%] and 324 [71.1%] for Kd56 vs. Vd, respectively), the exposure-adjusted incidence of Grade ≥3 AEs was also lower in the Kd56 group than in the Vd group (162.31 vs. 175.90). Overall, the long-term safety profile for Kd56 was acceptable, and there has been no evidence of cumulative toxicity with extended treatment.

Because of the relapsing nature of MM, and the availability of well tolerated agents, prolonged courses of maintenance therapy are now a standard of care in myeloma. Because maintenance lenalidomide confers a PFS and possibly an OS advantage compared with placebo in treatment of first-line MM[8-10] and when lenalidomide-dexamethasone is compared with dexamethasone,[11,12] lenalidomide-dexamethasone is becoming a standard first-line treatment, and therefore might not be an option for patients at relapse.[10] The ENDEAVOR trial was designed to offer RRMM patients an alternate doublet therapy until progression or intolerance. These results, showing tolerability and a survival benefit, support the emerging role of prolonged PI therapy.

Conclusion

With additional follow-up, clinically meaningful OS improvements continue to be observed with Kd56 versus Vd, including in key patient subgroups. The benefit-risk profile of Kd56 with longer-term data continued to provide support for its use as a standard of care in patients with RRMM.

Clinical Practice Points

- Extending OS is a major therapeutic goal for MM agents. PIs, such as bortezomib or carfilzomib, are a backbone therapy in MM treatment.
- In a prespecified interim analysis (data cutoff January 3, 2017) of the randomized phase III ENDEAVOR study, Kd56 significantly improved OS over Vd in patients with RRMM.
- Herein we report updated ENDEAVOR OS and safety data using a more recent data cutoff of July 19, 2017, when all patients had received at least 3 years of follow-up.
- Median OS was extended by 9 months with Kd56 versus Vd. These OS benefits were consistent across all subgroups examined, including patient age, cytogenetic risk, previous lenalidomide exposure, and lenalidomide-refractory status.
- Safety data were consistent with previous analyses.
- These longer-term data continue to provide support for the use of Kd56 as a standard of care in patients with RRMM.

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Supplemental Data

The supplemental table accompanying this article can be found in the online version at https://doi.org/10.1016/j.clml.2019.04.018.

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Supplemental Data

Supplemental Table 1 Subsequent Antimyeloma Therapies According to Age Group in ≥10% of Patients (ITT Population)

	<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)
Patients Treated With at Least 1 Antimyeloma Therapy, n (%)	150 (67.3)	143 (68.1)	101 (61.6)	125 (66.1)	40 (51.9)	33 (50.0)
Dexamethasone	110 (49.3)	115 (54.8)	71 (43.3)	92 (48.7)	28 (36.4)	23 (34.8)
Lenalidomide	77 (34.5)	87 (41.4)	44 (26.8)	62 (32.8)	16 (20.8)	16 (24.2)
Cyclophosphamide	53 (23.8)	65 (31.0)	34 (20.7)	35 (18.5)	12 (15.6)	14 (21.2)
Pomalidomide	43 (19.3)	50 (23.8)	29 (17.7)	47 (24.9)	10 (13.0)	10 (15.2)
Bortezomib	59 (26.5)	32 (15.2)	44 (26.8)	20 (10.6)	15 (19.5)	5 (7.6)
Melphalan	29 (13.0)	32 (15.2)	19 (11.6)	20 (10.6)	5 (6.5)	4 (6.1)
Thalidomide	27 (12.1)	34 (16.2)	9 (5.5)	23 (12.2)	3 (3.9)	3 (4.5)
Prednisone	8 (3.6)	11 (5.2)	10 (6.1)	20 (10.6)	4 (5.2)	5 (7.6)

Abbreviations: ITT = intent-to-treat; Kd56 = carfilzomib (56 mg/m^2) and dexamethasone; Vd = bortezomib and dexamethasone.