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Efficacy of Carfilzomib and Dexamethasone in Lenalidomide-Exposed and Refractory Multiple Myeloma Patients: Combined Analysis of Carfilzomib Trials

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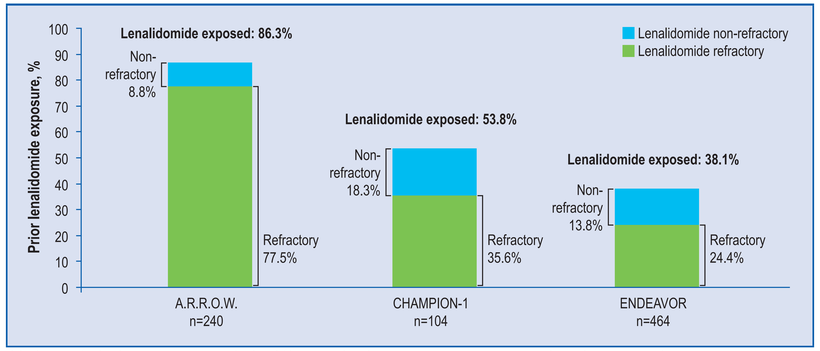
INTRODUCTION

- The introduction of proteasome inhibitors, immunomodulatory agents, and monoclonal antibodies have improved multiple myeloma (MM) outcomes; however, patients eventually relapse or become refractory to treatment, highlighting the importance of offering the most effective therapeutic approaches[1,2]
- The immunomodulatory agent lenalidomide in combination with dexamethasone (Rd) has been approved for the treatment of patients with relapsed or refractory multiple myeloma (RRMM) who received at least one prior therapy based on phase 3 trials showing improvements in clinical outcomes in patients receiving Rd versus dexamethasone alone (d)[3-5]
  - Rd is hence considered a reference regimen and has been used as the control arm in studies in which novel triplet regimens for RRMM were evaluated[6-9]
- Lenalidomide therapy has improved survival in transplant-ineligible newly diagnosed multiple myeloma (NDMM) patients receiving continuous Rd therapy and improved progression-free survival (PFS) in NDMM patients receiving maintenance lenalidomide following autologous stem cell transplantation[10-13]
- Based on these findings, lenalidomide is often part of therapy for transplant-ineligible and transplant-eligible NDMM patients
- With increasing use of lenalidomide in MM induction and maintenance therapy, resistance to lenalidomide is an emerging clinical challenge
- There is a need for active regimens in MM that has relapsed during or after lenalidomide treatment
- Carfilzomib (K) is a second-generation proteasome inhibitor that is approved as a single agent and as combination therapy with Rd (KRd) or d (Kd) for the treatment of patients with RRMM who have received 1–3 prior lines of therapy
- KRd and Kd have improved PFS and overall survival (OS) in RRMM[6,14-16]
- Because lenalidomide therapy has recently moved into the frontline setting, lenalidomide-refractory patients at first relapse are underrepresented in recent pivotal trials[6-9,14]
- Here, we present a post-hoc analysis of outcomes for lenalidomide-exposed and lenalidomide-refractory patients treated with Kd on the registrational trials CHAMPION-1 (NCT01677858), ENDEAVOR (NCT01568866), and A.R.R.O.W. (NCT02412878)

METHODS

- Efficacy data from patients enrolled in the phase 1/2 CHAMPION-1 and phase 3 ENDEAVOR and A.R.R.O.W. trials were pooled to evaluate PFS and response rates to Kd doublet therapy for those who had previous exposure or were refractory to lenalidomide treatment
- Patients with 2–3 prior lines of therapy were enrolled in A.R.R.O.W while patients with 1–3 prior lines of therapy were enrolled in CHAMPION-1 and ENDEAVOR. The proportion of patients treated with Kd who had prior exposure to lenalidomide in each of the 3 trials is presented in the Figure
- Patients were refractory to any prior lenalidomide treatment if there was at least one prior lenalidomide regimen where the best response was stable disease or progressive disease, or the relapse/progression date associated with the regimen was within 60 days of the stop date for that regimen
- The once-weekly Kd dosing schedule in A.R.R.O.W. and CHAMPION-1, and the twice-weekly Kd dosing schedule in ENDEAVOR have been previously described[14,17,18]
- Patients who received once-weekly Kd at 70 mg/m^2 in A.R.R.O.W. and CHAMPION-1, and patients who received twice-weekly Kd at 56 mg/m^2 in ENDEAVOR were included in the analysis
- Due to differences in patient populations in the 3 trials, patients were assigned to a group according to prior lines of therapy and lenalidomide exposure for this analysis:
  1. Combined CHAMPION-1 and ENDEAVOR patient population with 1 prior line of therapy and previously exposed to lenalidomide (n=71)
  2. Combined CHAMPION-1 and ENDEAVOR patient population with 1 prior line of therapy and refractory to lenalidomide (n=32)
  3. Combined A.R.R.O.W, CHAMPION-1, and ENDEAVOR patient population with 1–3 prior lines of therapy and previously exposed to lenalidomide (n=440)
  4. Combined A.R.R.O.W., CHAMPION-1, and ENDEAVOR patient population with 1–3 prior lines of therapy and refractory to lenalidomide in any line of previous therapy (n=336)
  5. Combined A.R.R.O.W., CHAMPION-1, and ENDEAVOR patient population with 2–3 prior lines of therapy and refractory to lenalidomide in the last line of therapy (n=228)

Figure. Proportion of Kd-treated patients with prior lenalidomide exposure in the A.R.R.O.W., CHAMPION-1, and ENDEAVOR trials



Patients were refractory to any prior lenalidomide treatment if there was at least one prior lenalidomide regimen where the best response was stable disease or progressive disease, or the relapse/progression date associated with the regimen was within 60 days of the stop date for that regimen. Percentages of lenalidomide exposed patients in A.R.R.O.W. correspond to the once-weekly Kd arm.
Kd, carfilzomib and dexamethasone.

RESULTS

Efficacy (Table)

- Median PFS was 15.6 months in lenalidomide-exposed and lenalidomide-refractory patients treated with Kd at first relapse
- For lenalidomide-exposed patients treated with Kd at first, second, or third relapse, median PFS was 11.3 months (95% confidence interval [CI], 10.0–13.2)
- Median PFS was 9.6 months (95% CI, 7.9–11.3) in lenalidomide-refractory patients treated with Kd at first, second, or third relapse
- Median PFS was 10.2 months (95% CI, 7.9–12.4) when patients with 2–3 prior lines of therapy who were refractory to lenalidomide in the last line of therapy were treated with Kd

Table. PFS and response rates in the pooled carfilzomib patient populations

Groups	1	2	3	4	5
	1 prior line, lenalidomide exposed[a] (n=71)	1 prior line, lenalidomide refractory[b] (n=32)	1–3 prior lines, lenalidomide exposed[c] (n=440)	1–3 prior lines, lenalidomide refractory (any prior)[d] (n=336)	2–3 prior lines, lenalidomide refractory (immediate prior)[e] (n=228)
Median PFS, months (95% CI)	**15.6** (14.1–21.0)	**15.6** (9.6–NE)	**11.3** (10.0–13.2)	**9.6** (7.9–11.3)	**10.2** (7.9–12.4)
PFS rate at 18 months, % (95% CI)	**49.8** (31.0–66.0)	**43.1** (16.0–68.0)	**35.5** (29.3–41.8)	**29.4** (22.6–36.4)	**30.1** (21.8–38.8)
Median follow-up, months (95% CI)	**11.4** (10.7–13.6)	**11.2** (9.3–14.2)	**12.1** (11.3–13.2)	**12.1** (11.4–13.5)	**12.1** (11.3–13.8)
ORR, % (95% CI)	**85.9** (75.6–93.0)	**81.3** (63.6–92.8)	**67.0** (62.4–71.4)	**62.5** (57.1–67.7)	**61.4** (54.8–67.8)
≥CR, %	15.5	12.5	8.9	6.8	7.0
≥VGPR, %	62.0	53.1	39.5	35.4	36.4

[a]CHAMPION-1 and ENDEAVOR combined population with 1 prior line of therapy and lenalidomide exposed.
[b]CHAMPION-1 and ENDEAVOR combined population with 1 prior line of therapy and lenalidomide refractory.
[c]Patients from A.R.R.O.W., CHAMPION-1, and ENDEAVOR with 1–3 prior lines of therapy and lenalidomide exposed.
[d]Patients from A.R.R.O.W., CHAMPION-1, and ENDEAVOR with 1–3 prior lines of therapy and lenalidomide refractory in any prior line.
[e]Patients from A.R.R.O.W., CHAMPION-1, and ENDEAVOR with 2–3 prior lines of therapy and lenalidomide refractory in the immediate prior line.
Disease assessment was based on independent review committee for ENDEAVOR, Onyx Response Computational Assessment for A.R.R.O.W., and the investigator for CHAMPION-1.
CI, confidence interval; CR, complete response; NE, not estimable; ORR, overall response rate; PFS, progression-free survival; VGPR, very good partial response.

Limitation of Study

- Because the lenalidomide dose that patients had received prior to study entry was not collected in the A.R.R.O.W., CHAMPION-1, and ENDEAVOR clinical trial databases, it was not possible to separately assess outcomes for patients refractory to a therapeutic lenalidomide dose or regimen versus those refractory to maintenance single-agent lenalidomide at low dose

CONCLUSIONS

- **This post-hoc analysis demonstrated that the Kd doublet is effective in MM patients relapsing on or after treatment with lenalidomide, including among patients who are refractory to lenalidomide**
- **In this pooled analysis, the median PFS of 15.6 months and overall response rate (ORR) of 81.3% in lenalidomide-refractory patients treated with Kd at first relapse are comparable in magnitude to the median PFS and ORR reported in lenalidomide-refractory patients treated with the triplet regimen pomalidomide plus bortezomib and dexamethasone (PVd) at first relapse in the phase 3 OPTIMISMM trial (median PFS for PVd: 17.8 months; ORR, 85.9%)[19]**
  - **Additionally, the median PFS of 11.3 months for Kd in lenalidomide-exposed patients with 1–3 prior lines of therapy is similar to the median PFS of 11.2 months reported for PVd in the lenalidomide-exposed population with 1–3 prior therapies[20]**
- **Efficacy of the Kd doublet in lenalidomide-refractory patients at last prior line of therapy is comparable to that reported for the triplet regimen daratumumab, bortezomib, and dexamethasone (DVd) in lenalidomide-refractory patients at the last line of treatment in the CASTOR study (median PFS: Kd, 10.2 months; DVd; 9.3 months)[21]**
- **Encouraging data from the phase 1b MMY1001 study show a median PFS of 14.1 months and median OS of 21.1 months in lenalidomide-refractory patients treated with Kd plus daratumumab[22]**
- **Kd has also demonstrated prolonged OS in lenalidomide-refractory RRMM patients (median OS, Kd vs Vd: 29.2 months vs 21.4 months; HR=0.86)[23]**
- **Based on the notable efficacy of Kd, this doublet therapy should be considered as a lenalidomide-sparing treatment option for patients with RRMM**

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ACKNOWLEDGEMENTS

This study was supported by Amgen Inc. The authors acknowledge Jacqueline Sayyah, PhD, of Amgen Inc. for medical writing support.

DISCLOSURES

M-VM has received consulting fees from, and has membership on an entity's Board of Directors or has served on advisory committees for, AbbVie, Amgen, GSK, Takeda, Janssen, and Celgene; has received honoraria from Amgen, Takeda, Janssen, and Celgene. **JGB** has received research funding from Genentech, Bluebird, BMS, Takeda, Janssen, Amgen, Celgene, Glenmark, Novartis, Teva, Sanofi, and Poseida Therapeutics, Inc. **MD** has received honoraria from Amgen, BMS, Takeda, Celgene, and Janssen. **DS** has received consulting fees from Takeda, Karyopharm, Merck, Celgene, Janssen, BMS, and Amgen; has received honoraria from Takeda, Karyopharm, Merck, Celgene, Janssen, BMS, Novartis, and Amgen; has received research funding from Celgene; has served on speakers bureau for Takeda, Merck, Celgene, Janssen, BMS, Novartis, and Amgen. **PJH** has received honoraria from Novartis, Janssen, Amgen, and Takeda; has received other (travel to meeting) from Takeda and Celgene. **MH** and **AZ-K** are are employees of, and own stock in, Amgen. MS is an employee of Amgen. **ASK** is an employee of Amgen; has stock in Amgen and WindMIL Therapeutics. **KW** has received consulting fees from Sanofi, Amgen, Celgene, Takeda, Janssen, BMS, and Juno; has received honoraria from Amgen, Takeda, Janssen, and BMS; has received research funding from Sanofi, Amgen, and Janssen.

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Carfilzomib in Relapsed or Refractory Multiple Myeloma Patients With Early or Late Relapse Following Prior Therapy: An Analysis of Overall Survival in Subgroups From the Randomized Phase 3 ASPIRE and ENDEAVOR Trials

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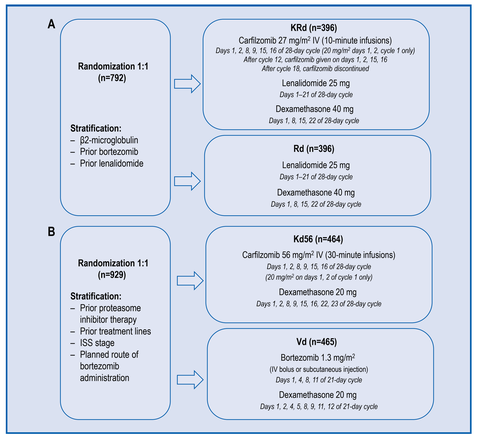
INTRODUCTION

- Carfilzomib is an irreversible proteasome inhibitor with proven efficacy as a single agent and in doublet and triplet combinations for the treatment of patients with relapsed or refractory multiple myeloma (RRMM)[1–6]
- The phase 3 ASPIRE (carfilzomib, lenalidomide, and dexamethasone [KRd] vs lenalidomide and dexamethasone [Rd])[2,3] and ENDEAVOR (carfilzomib [56 mg/m^2] and dexamethasone [Kd56] vs bortezomib and dexamethasone [Vd])[4,5] trials demonstrated that treatment with carfilzomib-based regimens led to superior efficacy outcomes (progression-free survival [PFS], overall survival [OS], overall response rate [ORR], and rate of complete response or better) compared with standard regimens in patients with RRMM (1–3 prior lines of therapy)
  - In ASPIRE, KRd improved OS compared with Rd (median, 48.3 months vs 40.4 months; hazard ratio [HR], 0.79 [95% confidence interval (CI), 0.67–0.95]; *P*=0.0045)[3]
  - In ENDEAVOR, Kd56 improved OS compared with Vd (median, 47.6 months vs 40.0 months; HR, 0.79 [95% CI, 0.65–0.96]; *P*=0.010)[5]
- Early relapse following initial MM therapy indicates a more aggressive disease and is a predictor of poor prognosis, irrespective of depth of response to initial therapy.[7] In RRMM treatment, it is important to understand the efficacy and safety of novel and effective agents when given at early or late relapse[8]
- A previous subgroup analysis found that carfilzomib-based regimens improved PFS and ORR over controls in ASPIRE and ENDEAVOR, regardless of whether patients experienced an early (≤1 year) or late (>1 year) relapse following the immediate prior therapy. Safety results were similar between early and late relapse groups in both studies[8]
- Here we performed post hoc analyses of ASPIRE and ENDEAVOR to assess OS and updated safety in the ASPIRE and ENDEAVOR early or late relapse subgroups

METHODS

- ASPIRE (ClinicalTrials.gov, number NCT01080391) and ENDEAVOR (ClinicalTrials.gov, number NCT01568866) were phase 3, randomized, multicenter, open-label trials that enrolled adult patients with RRMM who had received 1 to 3 prior lines of therapy
- In ASPIRE, patients were randomized 1:1 to receive KRd or Rd **(Figure 1A)**; in ENDEAVOR, patients were randomized 1:1 to receive Kd56 or Vd **(Figure 1B)**
  - Treatment was administered until disease progression, unacceptable toxicity, or withdrawal of consent in both studies. In ASPIRE, carfilzomib was reduced after 12 cycles and completely discontinued after cycle 18 (after which patients only received Rd)
- In this subgroup analysis, OS and safety in ASPIRE and ENDEAVOR were assessed by treatment arm and time to relapse (early vs late) from start of the most recent prior line of therapy
  - Early relapse was defined as a relapse ≤1 year after initiating the most recent prior line of therapy (as assessed by investigator), while a late relapse was defined as a relapse occurring after 1 year[7]
- The cutoff dates for this subgroup analysis of OS were April 28, 2018 for ASPIRE, corresponding with the final OS analysis,[3] and July 19, 2017 for ENDEAVOR, corresponding with the updated 3-year OS analysis
- Disease progression and treatment response were evaluated using the International Myeloma Working Group Uniform Response Criteria,[9] with ORR defined as the percentage of patients achieving a partial response or better
- OS and PFS were summarized via Kaplan–Meier methods; HRs for OS and PFS were estimated using unstratified Cox proportional hazards models
- For the safety analysis, patients were included if they had received ≥1 dose of study treatment. Adverse events (AEs) were coded using Medical Dictionary for Regulatory Activities and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03
- In this post hoc analysis, *P* values were calculated for exploratory purposes

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



ISS, International Staging System; IV, intravenous; Kd56, carfilzomib (56 mg/m^2) and dexamethasone; KRd, carfilzomib, lenalidomide, and dexamethasone; Rd, lenalidomide and dexamethasone; Vd, bortezomib and dexamethasone.

RESULTS

- Baseline characteristics were generally similar for carfilzomib-based and control regimens in ASPIRE and ENDEAVOR **(Table 1)**[8]
  - In ASPIRE, 29% of KRd patients and 26% of Rd patients experienced relapse ≤1 year from initiating the most recent prior line of therapy
  - In ENDEAVOR, 27% of Kd56 patients and 25% of Vd patients experienced relapse ≤1 year from initiating the most recent prior line of therapy
  - A greater percentage of patients with early versus late relapse had prior bortezomib (74.7% vs 61.7%) or lenalidomide therapy (23.0% vs 18.7%) in ASPIRE, high-risk cytogenetics (31.4% vs 19.9%) in ENDEAVOR, and 3 prior regimens in ASPIRE (35.9% vs 17.2%) and ENDEAVOR (27.6% vs 13.8%) at baseline

Table 1. Patient Baseline Demographic and Clinical Characteristics[a]

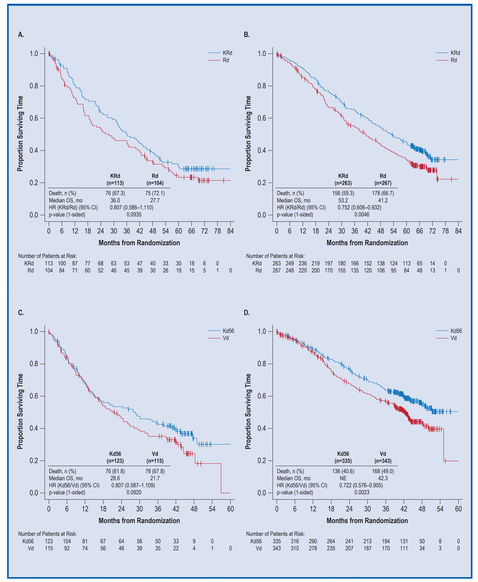
	ASPIRE				ENDEAVOR			
	Early Relapse		Late Relapse		Early Relapse		Late Relapse	
	KRd (n=113)	Rd (n=104)	KRd (n=263)	Rd (n=267)	Kd56 (n=123)	Vd (n=116)	Kd56 (n=335)	Vd (n=340)
Age, median years (range)	64.0 (41–85)	65.0 (40–87)	64.0 (38–87)	65.0 (31–91)	64.0 (35–82)	65.0 (42–85)	65.0 (36–89)	66.0 (30–88)
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 and/or 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 (%)[b]								
<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 (%)[c]								
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)

FISH, fluorescence in-situ hybridization; Kd56, carfilzomib (56 mg/m^2) and dexamethasone; KRd, carfilzomib, lenalidomide, and dexamethasone; Rd, lenalidomide and dexamethasone; Vd, bortezomib and dexamethasone.
In ASPIRE, high-risk patients had genetic subtype t(4;14) or t(14;16) or deletion 17p in ≥60% of plasma cells, while standard-risk patients did not have t(4;14) or t(14;16) and had deletion 17p in <60% of plasma cells. In ENDEAVOR, high-risk patients had genetic subtype t(4;14) or t(14;16) in ≥10%, or deletion 17p in ≥20%, of screened plasma cells, while standard-risk patients were those without these genetic subtypes.
[a]Previously published in Mateos et al 2018[8]; [b]Per Interactive Voice Response System; [c]Two patients in the ASPIRE early relapse group (KRd, n=1; Rd, n=1) and one patient in the ENDEAVOR early relapse group (Vd) had 4 prior therapies.

Efficacy

- In ASPIRE, median OS for patients with early relapse was 8.3 months longer for the KRd versus Vd group (36.0 months vs 27.7 months; HR, 0.81 [95% CI, 0.59–1.11]) **(Figure 2A)**
  - For patients with late relapse in ASPIRE, median OS was 12.0 months longer for the KRd versus Rd group (53.2 months vs 41.2 months; HR, 0.75 [95% CI, 0.61–0.93]) **(Figure 2B)**
- In ENDEAVOR, median OS for patients with early relapse was 6.9 months longer for the Kd56 versus Vd group (28.6 months vs 21.7 months; HR, 0.81 [95% CI, 0.59–1.11]) **(Figure 2C)**
  - For patients with late relapse in ENDEAVOR, median OS was not evaluable (NE) for Kd56 versus 42.3 months for Vd (HR, 0.72 [95% CI, 0.58–0.91]) **(Figure 2D)**
- PFS and ORR improved with carfilzomib-based regimens compared with controls in both ASPIRE and ENDEAVOR regardless of whether patients had an early or late relapse **(Figure 3; Table 2)**

Figure 2. Overall Survival in the ASPIRE and ENDEAVOR Trials for Patients with Early vs Late Relapse. (A) OS in ASPIRE for Patients with Early Relapse (B) OS in ASPIRE for Patients with Late Relapse (C) OS in ENDEAVOR for Patients with Early Relapse (D) OS in ENDEAVOR for Patients with Late Relapse



CI, confidence interval; HR, hazard ratio; Kd56, carfilzomib (56 mg/m^2) and dexamethasone; KRd, carfilzomib, lenalidomide, and dexamethasone; NE, not evaluable; OS, overall survival; Rd, lenalidomide and dexamethasone; Vd, bortezomib and dexamethasone.

Safety

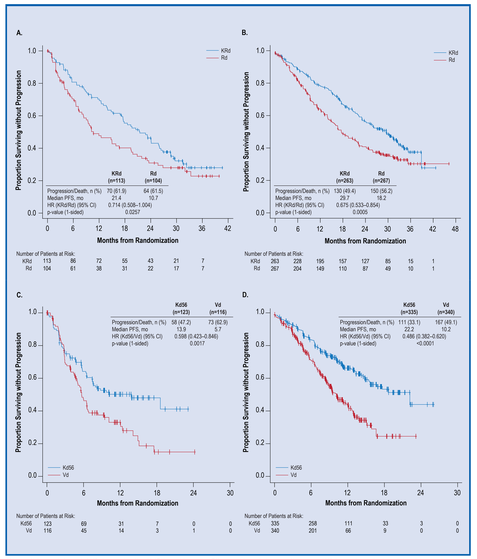
- Grade ≥3 treatment-emergent adverse events (TEAEs) in ASPIRE occurred in 89.3% (KRd) versus 82.0% (Rd) of patients with an early relapse and 86.9% (KRd) versus 83.0% (Rd) of patients with a late relapse **(Table 3)**
- Grade ≥3 TEAEs in ENDEAVOR occurred in 77.0% (Kd56) versus 77.0% (Vd) of patients with early relapse and 83.6% (Kd56) versus 69.0% (Vd) of patients with late relapse **(Table 3)**

Table 2. Efficacy Outcomes in Early vs Late Relapse Subgroups

	ASPIRE				ENDEAVOR			
	Early Relapse		Late Relapse		Early Relapse		Late Relapse	
	KRd (n=113)	Rd (n=104)	KRd (n=263)	Rd (n=267)	Kd56 (n=123)	Vd (n=116)[b]	Kd56 (n=335)	Vd (n=340)[c]
Median OS, months	36.0	27.7	53.2	41.2	28.6	21.7	NE	42.3
HR for KRd vs Rd (ASPIRE) or Kd56 vs Vd (ENDEAVOR) (95% CI)	0.807 (0.586–1.110)		0.752 (0.606–0.932)		0.807 (0.587–1.109)		0.722 (0.576–0.905)	
Median PFS, months[a]	21.4	10.7	29.7	18.2	13.9	5.7	22.2	10.2
HR for KRd vs Rd (ASPIRE) or Kd56 vs Vd (ENDEAVOR) (95% CI)	0.714 (0.508 –1.004)		0.675 (0.533–0.854)		0.598 (0.423–0.846)		0.486 (0.382–0.620)	
Best overall response, n (%)[a]								
CR+	25 (22.1)	8 (7.7)	97 (36.9)	27 (10.1)	8 (6.5)	4 (3.4)	50 (14.9)	25 (7.4)
VGPR+	72 (63.7)	32 (30.8)	194 (73.8)	116 (43.4)	50 (40.7)	24 (20.7)	198 (59.1)	105 (30.9)
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)

CI, confidence interval; Kd56, carfilzomib (56 mg/m^2) and dexamethasone; CR+, complete response or better; HR, hazard ratio; KRd, carfilzomib, lenalidomide, and dexamethasone; NE, not evaluable; OS, overall survival; PFS, progression-free survival; Rd, lenalidomide and dexamethasone; Vd, bortezomib and dexamethasone; VGPR+, very good partial response or better.
[a]Previously published in Mateos et al 2018[8]; [b]n=115 for OS data cut; [c]n=343 for OS data cut.

Figure 3. Progression-Free Survival in the ASPIRE and ENDEAVOR Trials for Patients with Early vs Late Relapse. (A) PFS in ASPIRE for Patients with Early Relapse (B) PFS in ASPIRE for Patients with Late Relapse (C) PFS in ENDEAVOR for Patients with Early Relapse (D) PFS in ENDEAVOR for Patients with Late Relapse[a]



CI, confidence interval; HR, hazard ratio; Kd56, carfilzomib (56 mg/m^2) and dexamethasone; KRd, carfilzomib, lenalidomide, and dexamethasone; PFS, progression-free survival; Rd, lenalidomide and dexamethasone; Vd, bortezomib and dexamethasone.
[a]Previously published in Mateos et al 2018.[8]

Table 3. Treatment-Emergent Adverse Events (Safety Population)

	ASPIRE				ENDEAVOR			
	Early Relapse		Late Relapse		Early Relapse		Late Relapse	
	KRd (n=112)	Rd (n=100)	KRd (n=260)	Rd (n=264)	Kd56 (n=122)	Vd (n=113)	Kd56 (n=335)	Vd (n=336)
Any grade AE, n (%)	112 (100.0)	96 (96.0)	254 (97.7)	260 (98.5)	121 (99.2)	113 (100.0)	330 (98.5)	331 (98.5)
Grade ≥3 AE	100 (89.3)	82 (82.0)	226 (86.9)	219 (83.0)	94 (77.0)	87 (77.0)	280 (83.6)	232 (69.0)
Serious AE	74 (66.1)	62 (62.0)	170 (65.4)	145 (54.9)	77 (63.1)	57 (50.4)	197 (58.8)	124 (36.9)
AE leading to treatment discontinuation	40 (35.7)	35 (35.0)	85 (32.7)	75 (28.4)	33 (27.0)	24 (21.2)	102 (30.4)	96 (28.6)
Fatal AE	19 (17.0)	16 (16.0)	25 (9.6)	23 (8.7)	10 (8.2)	9 (8.0)	21 (6.3)	13 (3.9)

AE, adverse event; Kd56, carfilzomib (56 mg/m^2) and dexamethasone; KRd, carfilzomib, lenalidomide, and dexamethasone; Rd, lenalidomide and dexamethasone; Vd, bortezomib and dexamethasone.
Treatment-emergent AEs are defined as any AE with an onset date from the first dose through 30 days after the last dose of any study drug.

CONCLUSIONS

- **RRMM patients who received carfilzomib-based regimens (KRd and Kd56) had longer median OS compared with those who received Rd and Vd, respectively, regardless of whether they had an early or late relapse following the most recent prior line of therapy**
- **As expected, outcomes were improved in patients with a late relapse. We found that early relapse was correlated to worse outcomes, similar to results from other studies.[7,10] Patients with late relapse had a numerically greater magnitude of OS benefit with KRd and Kd56 compared with control arms than patients with early relapse**
  - **In ASPIRE, median OS was improved by 8.3 months (HR, 0.81 [95% CI, 0.59–1.11]) among patients with early relapse and by 12.0 months among patients with late relapse (HR, 0.75 [95% CI, 0.61–0.93]) receiving KRd versus Rd**
  - **In ENDEAVOR, median OS was improved by 6.9 months among patients with early relapse receiving Kd56 versus Vd (HR, 0.81 [95% CI, 0.59–1.11]; among patients with late relapse, median OS was NE for Kd56 versus 42.3 months for Vd (HR, 0.72 [95% CI, 0.58–0.91])**
- **Safety results for the early and late relapse subgroups were consistent with those previously reported in ASPIRE and ENDEAVOR for the overall population[3,4]**
- **In conclusion, the findings from this subgroup analysis underscore the impressive efficacy of carfilzomib-based therapy for the treatment of patients with RRMM. The benefits of carfilzomib-based regimens were found to be consistent regardless of whether patients experienced an early or late relapse after the most recent prior line of therapy**

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ACKNOWLEDGMENTS

The ASPIRE and ENDEAVOR studies were supported by Amgen, Inc. Medical writing and editorial assistance was provided by BlueMomentum, an Ashfield Company, part of UDG Healthcare PLC, and funded by Amgen Inc.

DISCLOSURES

MVM has received honoraria from Janssen, Celgene, Amgen, and Takeda. **HG** has served on advisory boards for Adaptive Biotechnology, Amgen, BMS, Celgene, Janssen, Sanofi, Takeda; received honoraria from ArtTempi, BMS, Celgene, Chugai, Janssen, and Novartis; and received research funding from Amgen, BMS, Celgene, Chugai, Janssen, Sanofi, Mundipharma, Takeda, and Novartis. **JFS-M** has received consulting fees from Bristol-Myers Squibb, Celgene, Janssen, Millennium, Merck Sharp & Dohme, Novartis, Sanofi, Roche, and Amgen. **JB** is an employee of and owns stock in Amgen. **MO** is an employee of and owns stock in Amgen. **ZY** 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 Celgene, Janssen, Amgen, Takeda, Novartis, Karyopharm, Abbvie, BMS, Merck, Mundipharma, Roche, Incyte, and Gilead.

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