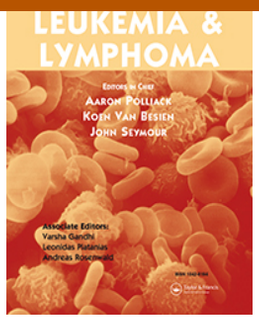

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ORIGINAL ARTICLE

Carfilzomib and dexamethasone versus eight cycles of bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma: an indirect comparison using data from the phase 3 ENDEAVOR and CASTOR trials

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ABSTRACT

In ENDEAVOR, carfilzomib and dexamethasone (Kd56) demonstrated significant improvement in progression-free survival (PFS) compared with bortezomib and dexamethasone (Vd). Both agents were administered until disease progression; the EU label for Vd, however, stipulates a maximum of eight treatment cycles. Here, matching-adjusted treatment comparison was used to compare efficacy of Kd56 with Vd, if Vd was administered for 8 cycles (Vd-8). Data from ENDEAVOR and CASTOR trials (which compared daratumumab, bortezomib, and dexamethasone with Vd-8) were used. Hazard ratios of PFS were estimated for Vd vs. Vd-8 and Kd vs. Vd-8. For cycles 1–8, risk reduction in PFS for Kd56 vs. Vd-8 was equal to that estimated in ENDEAVOR (HR: 0.53; 95% CI 0.44–0.65). Beyond eight cycles, risk reduction in PFS for Kd56 and Vd-8 was estimated to be 60% (HR: 0.40; 95% CI 0.26–0.63). The analysis suggested that PFS benefit of Kd56 over Vd increases when Vd is given for eight cycles only.

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KEYWORDS
Multiple myeloma; proteasome inhibitor treatment duration; matching-adjusted indirect treatment comparison

Introduction

The management of patients with multiple myeloma (MM) has evolved dramatically over the past decade owing to the introduction of more effective agents, such as proteasome inhibitors and immunomodulatory drugs [1,2]. More recently, monoclonal antibodies, such as elotuzumab and daratumumab, and the histone deacetylase inhibitor, panobinostat, have also been approved [3–5]. Among proteasome inhibitors, bortezomib (V) was the first agent to gain approval for the treatment of MM [6]. The combination of dexamethasone and bortezomib (Vd) has been established as a key regimen in the treatment of relapsed and/or refractory MM (RRMM) [7–9].

Carfilzomib (K) is a next-generation proteasome inhibitor that irreversibly binds to the proteasome, thus resulting in more sustained inhibition than with the reversible proteasome inhibitor V [9,10]. Carfilzomib is approved in Europe for use in combination with dexamethasone (Kd56; K administered at an ultimate dose of 56 mg/m^2), or with lenalidomide and dexamethasone (KRd; K administered at a dose of 27 mg/m^2) for the treatment of adults patients with MM who have received at least one prior therapy [11,12]. The approval of Kd56 was based on findings from the pivotal phase 3 randomized, controlled trial ENDEAVOR (NCT01568866), a head-to-head comparison of Kd56 with Vd in patients with RRMM. In order to have a direct head-to-head comparison that was not biased by a protocol-defined duration of treatment, Kd56 was compared with Vd under the same treatment schedule, that is: until disease progression, withdrawal of consent, or unacceptable toxicity [13,14]. Thus, in ENDEAVOR, the median (range) of Vd treatment duration was eight (5.0–15.0) cycles, with 25% of patients receiving 15 cycles. This is different from the treatment schedule in the

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bortezomib summary of product information and in other clinical trials where Vd is generally administered according to the European label, that is, for up to eight cycles only [15].

In the ENDEAVOR trial, Kd56 was superior to Vd for the primary outcome of progression-free survival (PFS), with 18.7 months vs. 9.4 months median PFS for Kd56 and Vd, respectively (hazard ratio (HR) 0.53; 95% confidence interval (CI) 0.44, 0.65, $p < .0001$) [13]. ENDEAVOR also demonstrated a significant improvement in overall survival (OS) for Kd56 over Vd (median OS 47.6 months vs. 40.0 months, HR 0.79; 95% CI 0.65, 0.96; $p = .010$) [14]. Adverse drug reactions were more frequently reported in patients who were receiving Kd56 than in those who were receiving Vd, including hypertension and cardiac failure. In contrast, the number of patients with peripheral neuropathy was significantly lower in the Kd56 group than in the Vd group [13,14]. It has been demonstrated that Kd56 is generally well tolerated and has a favorable benefit–risk profile [16].

The present analysis aims to characterize the clinical benefits of Kd56 vs. Vd by estimating the difference in efficacy and safety between Kd56 when given until disease progression and Vd administered for up to eight cycles as per the EU label. In the absence of direct head-to-head comparative data between Kd56 and Vd-8, this analysis was based on matching-adjusted indirect treatment comparisons (MAIC) using data from the ENDEAVOR trial and the phase 3 CASTOR trial, which compared daratumumab, bortezomib, and dexamethasone (DVd) with Vd-8 [17,18].

Materials and methods

Data

For the efficacy analysis, PFS data for Kd56 and Vd (until progression) from ENDEAVOR, and for Vd-8 from CASTOR (NCT02136134) were used. PFS was the primary outcome in both trials, and data from the longest published follow-up times were selected for inclusion in the analysis. In ENDEAVOR, the assessment of progression was based on the findings of an independent review committee at the first prespecified interim analysis, data cutoff 10 November 2014 (median follow-up 11.1 months (Vd) and 11.9 months (Kd56)) [13]. In CASTOR, the assessment of progression was based on a computerized algorithm and updated safety and efficacy data, cutoff 30 August 2017 (median follow-up 26.9 months) [18]. For the safety analysis of Kd56 vs. Vd-8, treatment-emergent adverse event (TEAE) data observed with Kd56 and Vd in ENDEAVOR were used (data cutoff 19 July 2017) [19].

ENDEAVOR and CASTOR study designs, patients, and treatments

The study designs and participant information of the ENDEAVOR [13] and CASTOR [17,20] trials have been described previously. In brief, both studies included adult patients with RRMM who had received one to three (ENDEAVOR) or at least one (CASTOR) previous line of therapy, who had achieved at least a partial response to a previous line of therapy, and who had adequate renal, hematological, and hepatic function. In ENDEAVOR, patients were randomized (1:1) to receive Kd56 ($n = 464$) or Vd ($n = 465$), administered during 28-day (Kd56) or 21-day (Vd) cycles [13]. In CASTOR, patients were randomized (1:1) to receive DVd ($n = 251$) or Vd-8 ($n = 247$), administered during 21-day cycles as described previously [17]. Treatment cycles were repeated eight times; in the DVd group, daratumumab was continued after cycle 8, until progressive disease [17]. Patients in the ENDEAVOR and CASTOR trials provided written informed consent, and the trials were conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines.

Efficacy analyses

PFS outcomes with Kd56 and Vd-8 were compared using a three-step modeling approach (Figure 1). In the first step, to minimize any confounding bias owing to observed differences across trial populations, patients receiving Vd in ENDEAVOR and patients receiving Vd-8 in CASTOR were matched for observed baseline characteristics using MAIC [21]. In the base case analysis, among all available variables, those considered to be predictive and prognostic factors for PFS and OS were selected for the matching. This approach is in agreement with the methods guide issued by the National Institute for Health and Care Excellence for population-adjusted indirect treatment comparisons [22]. The selected variables reflected disease characteristics and treatment history, and were generally consistent with validated prognostic markers currently used in stratifying patients into different risk groups [23,24]. Details of the variable selection process have been reported previously [25,26]. Table 1 presents an overview of parameters used for the MAICs.

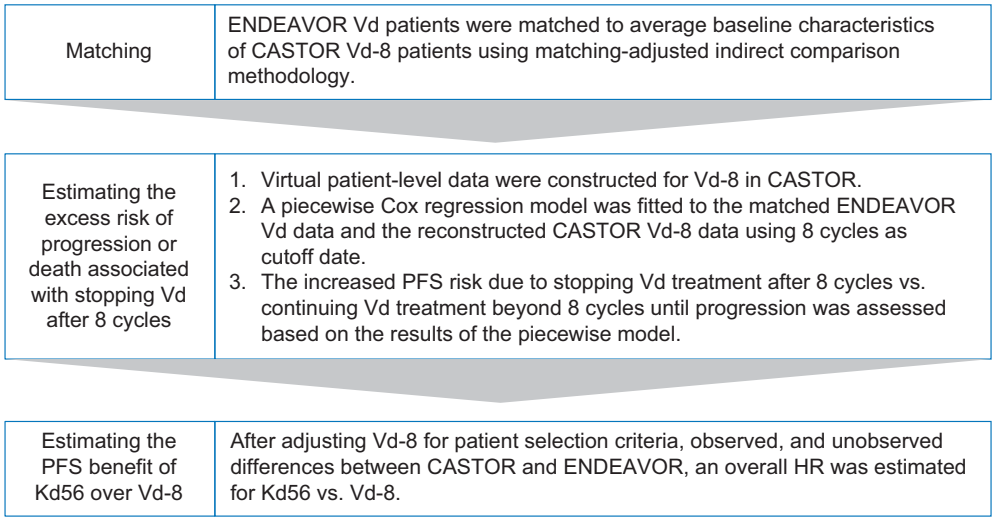

Figure 1. Summary of the stepwise modeling approach. HR: hazard ratio; Kd56: carfilzomib and dexamethasone; Vd: bortezomib and dexamethasone; Vd-8: bortezomib and dexamethasone given until eight cycles.

Table 1. Baseline characteristics of patients receiving Vd in ENDEAVOR and Vd-8 in CASTOR.

	Vd ENDEAVOR (before matching) (n= 465)	Vd ENDEAVOR (after matching)[a] (n= 378)[b]	Vd-8 CASTOR (n= 247)
Age, *n* (%)			
<65 years	210 (45.2%)	191 (50.6%)	125 (50.6%)
65–74 years	189 (40.6%)	133 (35.2%)	87 (35.2%)
75+ years	66 (14.2%)	54 (14.2%)	35 (14.2%)
Sex, *n* (%)			
Male	229 (49.2%)	184 (48.6%)	147 (59.5%)
International Staging System, *n* (%)[c]			
Stage 1	204 (44.1%)	147 (38.9%)	96 (38.9%)
Stage 2	151 (32.5%)	153 (40.5%)	100 (40.5%)
Stage 3	109 (23.4%)	78 (20.6%)	51 (20.6%)
Baseline creatinine clearance >60 mL/min, *n* (%)	297(63.9%)	264 (70.0%)	163 (70.0%)[d]
Type of multiple myeloma			
IgG	284 (61.1%)	230 (60.9%)	138 (55.9%)
Other	181 (38.9%)	148 (39.1%)	109 (44.1%)
Time since diagnosis in years, median	3.61	2.92	3.72
Patients with time since diagnosis ≥3.72 years (%)	47.6%	50.0%	50%
Number of prior therapies, *n* (%)			
1	232 (49.9%)	173 (45.7%)	113 (45.7%)
2	145 (31.2%)	113 (30.0%)	74 (30.0%)
3+	87 (18.9%)	92 (24.3%)	60 (24.3%)
Prior bortezomib, *n* (%)	252 (54.2%)	251 (66.4%)	164 (66.4%)
Prior IMID, *n* (%)	348(74.8%)	303 (80.2%)	198 (80.2%)
Prior lenalidomide	177 (38.1%)	155 (41.1%)	120 (48.6%)
Prior PI + IMID, *n (%)*	167 (35.9%)	189 (50.1%)	129 (52.2%)
Prior stem cell transplantation, *n* (%)	272 (58.5%)	228 (60.3%)	149 (60.3%)
Refractory to last prior therapy, *n* (%)	188 (40.4%)	130 (34.4%)	85 (34.4%)
Cytogenetic profile, *n* (%)			
Standard risk	291 (62.6%)	233 (61.7%)	135 (54.7%)
High risk	113 (24.3%)	93 (24.5%)	51 (20.6%)
Missing	61 (13.1%)	52 (13.8%)	61 (24.7%)

IMID: immunomodulatory imide drugs; PI: proteasome inhibitor; Vd: bortezomib and dexamethasone.
[a]Patients receiving Vd in ENDEAVOR were matched to patients receiving Vd-8 in CASTOR based on observed baseline characteristics using matching-adjusted indirect treatment comparison methodology. Base case matching analysis; the following variables were used for the matching: age (≥65, ≥75, other), time from diagnosis, International Staging System (2, 3, other), creatinine clearance (>60 mL/min, other), number of prior therapies (1, 2, other), prior stem cell transplantation (yes, no), prior bortezomib (yes, no), prior IMID (yes, no), and refractory to last prior therapy (yes, no).
[b]Sample size was calculated as the sum of weights.
[c]ISS measured at the start of treatment was used for matching.
[d]Based on 233 evaluable patients.

In the second step, in the absence of access to patient-level PFS data from the CASTOR trial, the published Kaplan–Meier curves were digitized to generate virtual patient-level CASTOR data that replicated the Kaplan–Meier curves [27]. Then, a piecewise Cox regression model was fitted to the matched ENDEAVOR Vd data and CASTOR Vd-8 data. In the piecewise Cox model, the cutoff date was determined at 24 weeks (corresponding to eight cycles of Vd). This model specification allowed separate HRs to be estimated for the first eight cycles, and for the treatment time beyond cycle 8. The HR for the first period captured all unobserved heterogeneity in baseline characteristics and between-trial differences between the matched PFS of ENDEAVOR Vd and the PFS of CASTOR Vd-8 (i.e. visually, the difference between the matched Vd and the Vd-8 PFS curves during the first eight cycles). The HR estimated for the period beyond eight cycles captured both unobserved heterogeneity and the impact of stopping Vd after eight cycles. Comparing these two HRs allowed the impact of unobserved heterogeneity to be quantified and subsequently the net impact of stopping Vd after eight cycles in ENDEAVOR to be quantified.

In the third step, adjusting for the between-trial differences in terms of patient selection criteria and observed baseline patient characteristics, as well as for unobserved differences between Vd-8 in CASTOR and Vd in ENDEAVOR, an overall HR was estimated for Kd56 vs. Vd-8 capturing the difference in the risk of progression or death during the first eight cycles and beyond eight cycles.

To assess the robustness of the results, three scenario analyses were explored: PFS for Vd in ENDEAVOR truncated at 16 months (i.e. where the number of patients at risk decreased below 5%), all available variables used for the matching, and no matching.

In addition, to assess whether continuing treatment, in particular Vd treatment, until progression leads to deeper responses over time than stopping treatment after eight cycles, cumulative proportions of patients in ENDEAVOR with a complete response (CR) or better, or with a very good partial response (VGPR) or better (for definitions of CR and VGPR, see [13]) were calculated for Kd56 and Vd from the start of the treatment.

Safety analyses

TEAEs (coded using MedDRA version 20.0) were analyzed based on the Kd56 and Vd safety data observed in ENDEAVOR [19]. For patients who were receiving Kd56, and for those receiving Vd for up to eight cycles, TEAEs with an onset date from the first dose until 30 days after the last dose of any study drug were included in the analysis. For patients who continued Vd beyond cycle 8, TEAEs with an onset date from cycle 9 to the last dose of any study drug were not included. Analysis of TEAEs included crude incidence proportions and exposure-adjusted incidences per treatment group; Kd56/Vd-8 exposure-adjusted incidence ratios and associated 95% CI were also calculated using the Poisson log-linear models.

Results

Efficacy analyses

To estimate the impact of stopping Vd after eight cycles on PFS, as a first step, patients who were receiving Vd in ENDEAVOR were matched to the baseline characteristics of those receiving Vd-8 in CASTOR. The observed baseline characteristics of patients receiving Vd in ENDEAVOR ($n = 465$) [13] and those receiving Vd-8 in CASTOR ($n = 247$) [18,20] have been published previously and are summarized in Table 1. In both trials, the median age was 64–65 years, 46–50% had received one line of prior therapy, and 50–54% had received two or more lines of prior therapy. Patients in the CASTOR trial had slightly more advanced disease (61% with International Staging System (ISS) scores $\geq$ 2) than those in ENDEAVOR (56% with ISS scores $\geq$2). Matching for observed baseline characteristics between the two trial populations meant that differences were effectively eliminated (Table 1).

After matching for observed baseline characteristics, a difference in PFS (up to and beyond eight cycles) was still evident between patients who were receiving Vd in ENDEAVOR and Vd-8 in CASTOR (Figure 2). This difference in PFS could be attributed to the unobserved heterogeneity in baseline characteristics, to between-trial heterogeneity that cannot be adjusted for by matching, and to stopping Vd after eight cycles. To assess the net impact of stopping Vd after eight cycles, the follow-up period was divided into two parts comprising cycles 1–8 and cycle 9 or more, respectively. For the period of cycles 1–8, during which any difference in PFS between the matched ENDEAVOR Vd and CASTOR Vd patients could be attributed to unobserved heterogeneity, the HR of PFS for ENDEAVOR Vd vs. CASTOR Vd was 1.36 (95% CI 1.01, 1.81). For the period of cycle 9 or more, during which a difference in PFS between the matched ENDEAVOR Vd and CASTOR Vd patients could be due to unobserved heterogeneity and the difference in Vd treatment

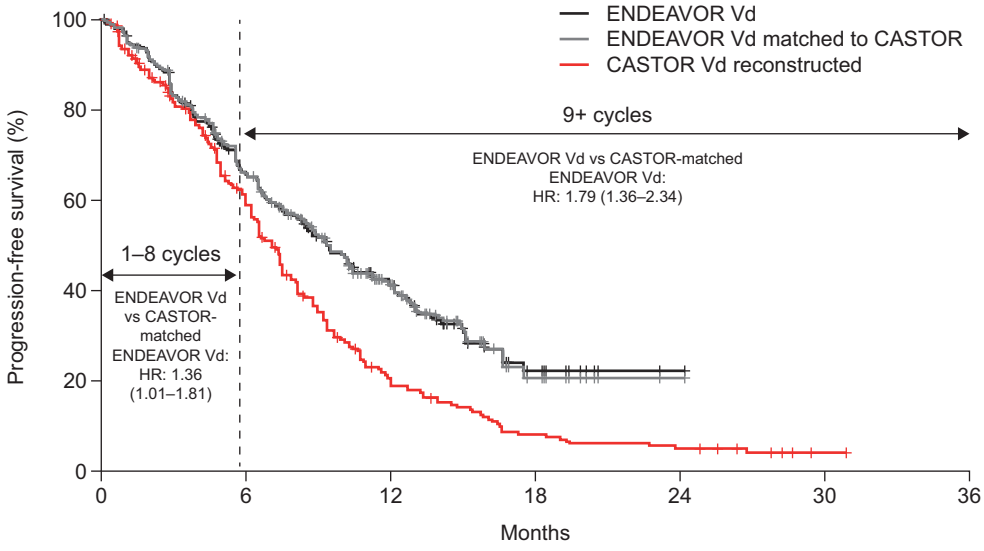

Figure 2. Impact on PFS of stopping Vd after eight cycles vs. continuing until progression. The HRs of PFS for the periods of cycles 1–8 cycles and cycles 9+ were estimated using a piecewise Cox regression model fitted to CASTOR-matched ENDEAVOR Vd data and reconstructed CASTOR Vd data. Vd cycle length was 21 days. CI: confidence interval; HR: hazard ratio; PFS: progression-free survival; Vd: bortezomib and dexamethasone.

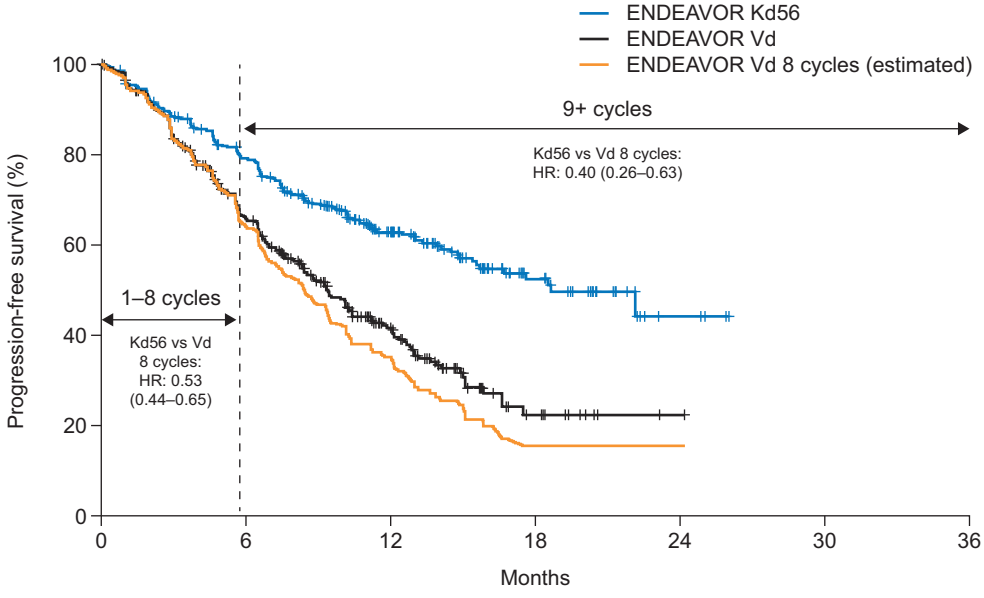

Figure 3. Difference in PFS with Kd56 vs. Vd eight cycles. The difference in PFS for Kd56 vs. Vd eight cycles was estimated using ENDEAVOR Vd data adjusted for the increased PFS risk associated with stopping Vd after eight cycles. Vd cycle length was 21 days. CI: confidence interval; HR: hazard ratio; Kd56: carfilzomib and dexamethasone; PFS: progression-free survival; Vd: bortezomib and dexamethasone.

duration, the HR of PFS for Vd ENDEAVOR vs. Vd CASTOR was 1.79 (95% CI 1.36, 2.34). The ratio between the two HRs provides an estimate of the net impact on PFS of stopping Vd treatment after eight cycles; thus, stopping Vd after eight cycles was estimated to increase the risk of progression or death by 32% compared with Vd treatment until progression (HR: 1.32; 95% CI 0.89, 1.96). The difference in PFS between Kd56 and Vd-8 was estimated, assuming Vd would have been stopped after eight cycles. For cycles 1–8, the risk reduction in PFS for Kd56 vs. Vd-8 cycles was equal to that estimated for Kd56 vs. Vd in ENDEAVOR (HR: 0.53; 95% CI 0.44, 0.65) [13]. Beyond eight cycles, the risk reduction in PFS for Kd56 and Vd-8 was estimated to be 60% (HR: 0.40; 95% CI 0.26, 0.63; Figure 3). The corresponding overall risk

Table 2. Excess risk of progression or death associated with stopping Vd after eight cycles vs. continuous Vd until progression, and efficacy of Kd56 vs. Vd-8.

Analysis	Excess risk of progression or death associated with stopping Vd after 8 cycles vs. Vd until progression	PFS HR for Kd56 vs. Vd-8
Base case analysis[a]	32% (–11%, 96%)	0.44 (0.30; 0.66)
Truncated PFS at 16 months	30% (–13%, 94%)	0.45 (0.30; 0.68)
All variables used for matching[b]	38% (–8%, 108%)	0.43 (0.29; 0.65)
No matching	41% (–3%, 106%)	0.43 (0.30; 0.61)

HR: hazard ratio; IMID: immunomodulatory imide drugs; Kd56: carfilzomib and dexamethasone; PFS: progression-free survival; PI: proteasome inhibitor; Vd: bortezomib and dexamethasone; Vd-8: bortezomib and dexamethasone given until eight cycles

[a]Base case covariates: age (≥65, ≥75, other), time from diagnosis, International Staging System (2, 3, other), creatinine clearance (>60 mL/min, other), number of prior therapies (1, 2, other), prior stem cell transplantation (yes, no), prior bortezomib (yes, no), prior IMID (yes, no), refractory to last prior therapy (yes, no).

[b]All available covariates: besides the covariates in the base case analysis, sex (male, female), type of multiple myeloma (IgG, other), prior lenalidomide (yes, no), prior PI + IMID (yes, no), and cytogenetic profile (standard risk, high risk, other).

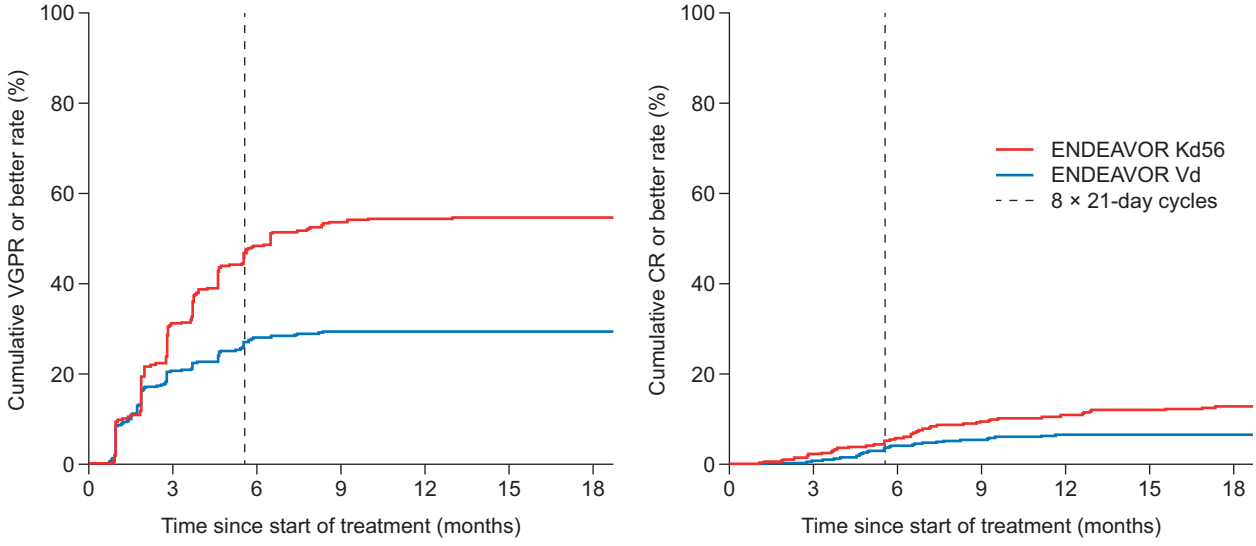

Figure 4. Cumulative rates of patients with a complete response or better or with a very good partial response or better with Kd56 and Vd in ENDEAVOR. Cumulative rate of CR or better or VGPR or better was assessed from the start of treatment in the safety population by an independent review committee (Kd: $n = 463$; Vd: $n = 456$). The time at which treatment for Vd eight cycles would be discontinued (i.e. at 8×21-day cycles) is indicated by a dashed line. CR: complete response; Kd56: carfilzomib and dexamethasone; Vd: bortezomib and dexamethasone arm; VGPR: very good partial response.

reduction, that is, capturing both the first eight cycles and the period beyond that, in a single measure, was 56% for Kd56 vs. Vd-8 (HR: 0.44; 95% CI 0.30, 0.66).

Similar results were obtained in scenario analyses. The excess risk of progression or death associated with stopping Vd after eight cycles vs. continuing Vd until progression was estimated to be between 30% and 41%. The overall risk reduction associated with Kd56 vs. Vd-8 was estimated to be between 0.43 and 0.45. Table 2 presents an overview of the results of the scenario analyses.

To assess whether the duration of treatment, in particular Vd treatment, had an impact on the depth of response, cumulative rates of CR or better and VGPR or better observed with Kd56 and Vd (given until progression) in ENDEAVOR were assessed (Figure 4). Over the entire treatment period, cumulative rates of both CR or better and VGPR or better were higher in patients receiving Kd56 than in those receiving Vd. During the first eight cycles, rates of CR or better and VGPR or better increased steadily for patients receiving Vd and started to become stable during subsequent cycles.

Safety analyses

Crude incidences and exposure-adjusted incidence rates of TEAEs in patients receiving Kd56 and Vd-8 in ENDEAVOR are shown in Table 3. Crude incidences tended to be higher in the Kd56 group than in the Vd-8 group. However, exposure-adjusted incidences per 100 person-years were lower with Kd56 than with Vd-8 for all TEAE categories assessed. Thus, after adjusting for exposure time, the risks of a grade 3 and

Table 3. Crude incidence proportions of TEAEs and exposure-adjusted incidence rates of TEAEs in Kd56 and Vd-8 patients in ENDEAVOR.

	Vd-8 (*N*= 456)			Kd56 (*N*= 463)			Kd56 vs. Vd-8
	Total person time (years)[a]	Total no. of patients with events (%)	Exposure-adjusted estimate per 100 patient-years (95% CI)	Total person time (years)[a]	Total no. of patients with events (%)	Exposure-adjusted estimate per 100 patient-years (95% CI)	Rate ratio: Kd56/Vd (95% CI)
Any TEAE	22.8	444 (97.4)	1947.37 (1774.40, 2137.20)	33.8	457 (98.7)	1352.07 (1233.62, 1481.89)	0.6943 (0.6093, 0.7912)
Grade ≥3 TEAE	114.8	294 (64.5)	256.10 (228.43, 287.11)	233.5	379 (81.9)	162.31 (146.77, 179.50)	0.6338 (0.5442, 0.7381)
Serious TEAEs	153.8	161 (35.3)	104.68 (89.70, 122.17)	413.4	279 (60.3)	67.49 (60.02, 75.89)	0.6447 (0.5310, 0.7827)
Grade ≥3 TEAEs leading to discontinuation of at least one study drug	157.3	144 (31.6)	91.54 (77.75, 107.79)	433.3	246 (53.1)	56.77 (50.10, 64.33)	0.6202 (0.5049, 0.7618)
TEAE leading to discontinuation of at least one study drug	174.4	104 (22.8)	59.63 (49.21, 72.27)	545.0	137 (29.6)	25.14 (21.26, 29.72)	0.4215 (0.3267, 0.5439)
TEAE leading to discontinuation of bortezomib or carfilzomib	177.6	91 (20.0)	51.24 (41.72, 62.93)	568.2	120 (25.9)	21.12 (17.66, 25.26)	0.4122 (0.3139, 0.5413)
Death owing to TEAE	181.4	20 (4.4)	11.03 (7.11, 17.09)	574.6	31 (6.7)	5.40 (3.79, 7.67)	0.4893 (0.2789, 0.8585)

CI: confidence interval; Kd56: carfilzomib and dexamethasone; TEAE: treatment-emergent adverse event; Vd: bortezomib and dexamethasone

TEAEs were defined as any adverse event with an onset date from the first dose through 30 days after the last dose of any study drug and were coded using MedDRA version 20.0. Patients were counted only once for each event of interest.

[a]Total person time is the sum of the time to first TEAE for all patients in each treatment group. If a patient had no event, the entire exposure time to study treatment was considered in the sum. For patients receiving Vd who continued study treatment beyond cycle 8, adverse events with an onset date from cycle 9 to the last dose of any study drug are not included. For patients with no events, the exposure time to study treatment was defined as the duration of the first eight cycles.

above or of a serious TEAE were estimated to be approximately 35% lower with Kd56 than with Vd-8. The risk of a TEAE leading to discontinuation of any, or both, study drugs was estimated to be approximately 60% lower with Kd56 than with Vd-8 (Table 3).

An additional safety analysis assessed specific TEAEs that had been previously found to be associated with Kd56 (cardiovascular events) or Vd (peripheral neuropathy, gastrointestinal toxicities) [13] (Table 4). The incidence of grade 2 or above, or grade 3 or above, peripheral neuropathies was lower in the Kd56 group than in the Vd-8 group. Likewise, the exposure-adjusted estimates indicated that rates were higher with Vd-8 than with Kd56 for diarrhea, nausea, and constipation. For the cardiovascular TEAEs of cardiac failure, hypertension, and embolic or thrombotic events, crude incidences and exposure-adjusted incidence rates per 100 person-years were higher in the Kd56 group than in the Vd-8 group for all three outcomes, but these findings were not statistically significant. The exposure-adjusted rate ratios were 1.18 (95% CI 0.66, 21.4), 1.81 (95% CI 1.26, 2.60), and 1.85 (95% CI 0.97, 3.52) for cardiac failure, hypertension, and embolic or thrombotic events, respectively.

Discussion

This exploratory analysis of ENDEAVOR that used MAIC methodology aimed to estimate the difference in efficacy with Kd56 vs. Vd-8. The results suggest that the benefit for PFS with Kd56 treatment over Vd treatment is larger if Vd is given for eight cycles only instead of continued until progression. Furthermore, the data suggest that a prolonged treatment duration of Vd improves PFS, thus adding to the growing body of evidence that there may be a benefit for patients receiving proteasome inhibitor treatment until progression rather than for a fixed number of cycles.

If Vd had been given for eight cycles, the risk of progression or death was estimated to be 56% lower with Kd56 than with Vd-8. This difference in PFS risk is greater than that observed in the original ENDEAVOR trial where Vd was administered until progression, and where the risk of progression or death was 47% lower with Kd56 than with Vd [13]. Scenario analyses suggested that the results were robust. A corresponding analysis for OS could not be performed, because survival data from the CASTOR trial were not as mature as PFS data at the time of this analysis.

Apart from the estimated difference between Kd56 and Vd-8, the findings of the present study may indicate that an extended duration of treatment with Vd,

Table 4. Crude incidence proportions and exposure-adjusted incidence rates of selected TEAE events in Kd56 and Vd-8 patients in ENDEAVOR.

	Vd-8 (*N* = 456)			Kd56 (*N* = 463)			Kd56 vs. Vd-8
Event of interest	Total person time (years)[a]	Total no. of patients with events (%)	Exposure-adjusted estimate per 100 patient-years (95% CI)	Total person time (years)[a]	Total no. of patients with events (%)	Exposure-adjusted estimate per 100 patient-years (95% CI)	Rate ratio: Kd56/Vd (95% CI)
Peripheral neuropathy (SMQN)							
SMQN peripheral neuropathy (grade ≥2)	153.3	140 (30.7)	91.32 (77.38, 107.78)	533.1	32 (6.9)	6.00 (4.24, 8.49)	0.0657 (0.0448, 0.0965)
SMQN peripheral neuropathy (grade ≥3)	175.9	39 (8.6)	22.17 (16.20, 30.35)	560.2	11 (2.4)	1.96 (1.09, 3.55)	0.0886 (0.0454, 0.1729)
Gastrointestinal toxicities							
Diarrhea	141.4	153 (33.6)	108.20 (92.35, 126.78)	379.6	170 (36.7)	44.78 (38.53, 52.05)	0.4139 (0.3327, 0.5149)
Nausea	163.9	66 (14.5)	40.27 (31.64, 51.26)	458.9	110 (23.8)	23.97 (19.88, 28.90)	0.5953 (0.4387, 0.8077)
Constipation	144.9	114 (25.0)	78.67 (65.48, 94.53)	500.9	75 (16.2)	14.97 (11.94, 18.78)	0.1903 (0.1422, 0.2547)
Vomiting	171.0	33 (7.2)	19.30 (13.72, 27.15)	504.8	79 (17.1)	15.65 (12.55, 19.51)	0.8109 (0.5402, 1.2174)
Cardiovascular toxicities							
SMQN cardiac failure	178.0	14 (3.1)	7.87 (4.66, 13.28)	546.5	51 (11.0)	9.33 (7.09, 12.28)	1.1865 (0.6568, 2.1434)
SMQN hypertension	168.8	36 (7.9)	21.33 (15.38, 29.57)	407.4	157 (33.9)	38.54 (32.96, 45.06)	1.8070 (1.2579, 2.5956)
SMQN embolic and thrombotic events	177.6	11 (2.4)	6.19 (3.43, 11.18)	514.8	59 (12.7)	11.46 (8.88, 14.79)	1.8504 (0.9721, 3.5222)

CI: confidence interval; Kd56: carfilzomib and dexamethasone; SMQN: standardized MedDRA query, narrow scope; TEAE: treatment-emergent adverse event; Vd: bortezomib and dexamethasone

TEAEs were defined as any adverse event with an onset date from the first dose through 30 days after the last dose of any study drug and were coded using MedDRA version 20.0. Patients were counted only once for each event of interest.

[a]Total person time is the sum of the time to first TEAE for all patients in each treatment group. If a patient had no event, the entire exposure time to study treatment was considered in the sum. For patients receiving Vd who continued study treatment beyond cycle 8, adverse events with an onset date from cycle 9 to the last dose of any study drug are not included. For patients with no events, the exposure time to study treatment was defined as the duration of the first eight cycles.

and possibly other proteasome inhibitors, beyond eight cycles could result in prolonged PFS. With V, it has been shown that proteasome function recovers within 72 hours after dosing, with no observed long-term effects on the proteasome [28,29] indicating that the efficacy of V could be related to both the duration of therapy and cumulative dose received. Several other recently published studies have also demonstrated that prolonged treatment with proteasome inhibitors or immunomodulatory drugs provides a benefit for patients [30–34]. Subcutaneous V, which has been shown to be as efficacious as intravenous V but to have a more favorable safety profile [35], should enable patients to receive longer treatment with less toxicity. Continuous treatment with proteasome inhibitors might lead to a benefit for improved outcomes, especially in high-risk patients, such as those with del[17/17p] cytogenic abnormalities [36]. Thus, the identification of patients who can tolerate continuous treatment with proteasome inhibitors might be of clinical value in the management of MM.

To identify possible drivers for the improved PFS benefit with a longer Vd treatment duration, cumulative response rates were assessed for patients receiving Kd56 and Vd in ENDEAVOR (both given until progression). Cumulative rates of CR or better and VGPR or better were consistently higher with Kd56 than with Vd, indicative of a greater depth of response with Kd56 than with Vd, an effect that is likely to contribute to the longer duration PFS with Kd56 than with Vd. In the Vd arm, rates of CR or better and VGPR or better continued to gradually increase after cycle 8, which may imply that the improved PFS with continued Vd treatment beyond eight cycles likely contributes to a greater depth of response. However, a carryover effect of the eight cycles administered previously cannot be excluded. Continued Vd treatment duration might also provide a benefit for PFS by maintaining the response achieved during the early cycles, whereas stopping Vd after eight cycles could increase the risk of relapse. In line with this hypothesis, in ENDEAVOR the median (range) duration of response to continued Vd was 10.4 (95% CI 9.3, 13.8), whereas it was 7.9 months (95% CI 6.7, 11.3) with eight cycles of Vd in CASTOR [13,17].

Using truncated data for patients who received more than eight cycles of Vd in ENDEAVOR the differences in the safety profiles of Kd56 and Vd given for eight cycles were estimated. For any TEAE, grade 3 or higher TEAEs, serious TEAEs, TEAEs leading to discontinuation, and fatal TEAEs, exposure-adjusted incidence rates were lower with Kd56 than with Vd-8. Consistent with previous findings, the estimated risk of peripheral

neuropathy was significantly higher with Vd given for eight cycles than with Kd56. Hypertension, a known and manageable side-effect with carfilzomib, was more frequent with Kd56 than with Vd-8. Cardiac failure and embolic and thrombotic events were also more frequent with Kd56 than with Vd-8.

Several factors should be considered when interpreting the present data. First, the analysis used MAIC methodology, which is considered less robust than a randomized controlled trial. Compared with other indirect treatment comparisons such as network meta-analyses that do not adjust for differences in trial design or patient populations and are thus susceptible to greater bias, MAIC is a more robust methodology and is considered more reliable by payers and health technology assessment authorities to fill any gaps in the available comparative evidence. Another limitation of the present study is that the follow-up durations were different between the ENDEAVOR data (median follow-up: 11.1 months (Vd group) and 11.9 months (Kd56 group)) and the CASTOR data (median follow-up: 19.4 months); however, this is due to PFS data from the longest published follow-up available at the time of the analyses being included, in order to achieve the most robust analysis. Moreover, the ENDEAVOR PFS Kaplan–Meier curves are mature up to about 16–18 months, allowing a reliable and robust comparison even beyond the first eight Vd cycles. Finally, patient-level data for Vd-8 had to be reconstructed, which inherently adds uncertainty to the reported results.

The methodological approach used in this study attempted to adjust for the differences in trial design, notably in this case Vd treatment duration, allowing cross-trial comparisons to be undertaken. Using this approach, the analyses suggested that, if Vd had been given for only eight cycles instead of continued until progression, the treatment benefit with Kd56 would have been larger, with lower HR than that observed in ENDEAVOR. Exposure-adjusted incidence rates of grade 3 or worse TEAEs were lower with Kd56 than with Vd. Overall, it was concluded that the duration of Vd treatment has a significant impact on both the response rates and duration of response, and that the relative efficacy and safety of Kd56 vs. Vd are increased when Vd treatment is provided as per label guidance.

Disclosure statement

K. Weisel has participated in advisory boards for Amgen, BMS, Celgene, Janssen, Juno, Sanofi, and Takeda; has received honoraria from Amgen, BMS, Celgene, Janssen, Novartis, and Takeda; and has received research funding from Amgen, Celgene, Janssen, and Sanofi. I. M. Majer is an employee of Amgen (Europe) GmbH and holds Amgen stocks. L. DeCosta is an employee of Amgen Ltd and holds Amgen Stocks. A. Oriol has been a member of advisory boards for Amgen, Janssen, and Takeda. H. Goldschmidt has received research support from Amgen, BMS, Celgene, Chugai, Janssen, Mundipharma, Novartis, Sanofi, and Takeda; has participated in advisory boards for Adaptive Biotechnology, Amgen, BMS, Celgene, Janssen, Sanofi, and Takeda; and has received honoraria for speakers' bureaux from ArtTempi, BMS, Celgene, Chugai, Janssen, and Novartis. H. Ludwig has received honoraria for speaker's bureau from Amgen, BMS, Celgene, Janssen, and Takeda, as well as research grants from Amgen and Takeda. M. Campioni is an employee of Amgen (Europe) GmbH and holds Amgen stocks. Z. Szabo is an employee of Amgen (Europe) GmbH and holds Amgen stocks. M. Dimopoulos received consulting fees from Abbvie, Amgen, Celgene, Janssen, and Takeda.

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