IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Carfilzomib (multiple myeloma) –

Addendum to Commission A17-38[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC	European Organisation for Research and Treatment of Cancer
FACT/GOG-Ntx	Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ISS	International Staging System
MID	minimally important difference
MMRM	mixed-effects model repeated measures
PFS	progression-free survival
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-MY20	Quality of Life Questionnaire-Multiple Myeloma Module 20
SAE	serious adverse event
SOC	System Organ Class
SPC	Summary of Product Characteristics

1 Background

On 9 January 2018, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A17-38 (Carfilzomib – Benefit assessment according to §35a Social Code Book V) [1].

In its dossier [2], the pharmaceutical company (hereinafter referred to as "the company") had presented results of the studies ASPIRE and ENDEAVOR for the assessment of the added benefit of carfilzomib in comparison with the appropriate comparator therapy (ACT).

In the dossier assessment, the ASPIRE study was used for the assessment of the combination of carfilzomib + lenalidomide + dexamethasone. However, no usable data were available for the outcome categories of morbidity, health-related quality of life, and side effects [1]. With its written comments [3], the company submitted further data on the ASPIRE study.

The results of the ENDEAVOR study were not used for the dossier assessment because it remained unclear for the comparator arm, in which treatment with bortezomib + dexamethasone was administered, whether patients were treated in compliance with the approval [1]. As a result of the written comments [3] and the discussion in the oral hearing [4], however, the inclusion criteria of the ENDEAVOR study were considered adequate and in line with the German health care context.

The G-BA commissioned IQWiG with the following assessments:

- assessment of the analyses on the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and Quality of Life Questionnaire-Multiple Myeloma Module 20 (QLQ-MY20) and on the outcome category of side effects, which were subsequently submitted by the company in the commenting procedure, and
- assessment of the ENDEAVOR study under consideration of the analyses on the questionnaires EORTC QLQ-C30 and QLQ-MY20 and on the outcome category of side effects presented by the company in the commenting procedure

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

Changes in comparison with Version 1.0

The present Version 1.1 of 1 February 2018 replaces Version 1.0 of the addendum of 26 January 2018. The following changes are contained in Version 1.1 compared with Version 1.0:

- In Version 1.0, in Table 3 and Table 5, information on the median survival time and on proportions of patients with event between the intervention arm and the comparator arm was interchanged for some outcomes. This was corrected in Version 1.1. The information provided on group differences (effect estimations, confidence intervals, and p-values) was already correct in Version 1.0.
- In Version 1.0, in Table 13, the unit for the outcome "overall survival" was erroneously given as "days" instead of "months". This was corrected in Version 1.1.

The result of the assessment was not affected by these changes.

2 Assessment

2.1 Assessment of the data on the ASPIRE study subsequently submitted

The research question of the benefit assessment was the assessment of the added benefit of carfilzomib in comparison with the ACT in adult patients with multiple myeloma who have received at least one prior therapy. In its dossier, the company presented the results of the ASPIRE study for the assessment of the added benefit of carfilzomib in combination with lenalidomide and dexamethasone versus the ACT lenalidomide in combination with dexamethasone. This study was used in dossier assessment A17-38.

The design of the study and the characteristics of the patients included were described in dossier assessment A17-38 [1].

For dossier assessment A17-38, no usable data on morbidity, health-related quality of life, and side effects were available for the assessment of the added benefit of carfilzomib on the basis of the ASPIRE study. With the dossier, the company had only presented analyses on selected subscales of the questionnaires EORTC QLQ-C30 and QLQ-MY20, which were recorded completely in the study. These were not used for the benefit assessment because selective reporting was possible. There were also no usable analyses for the outcomes "serious adverse events (SAEs)", "severe adverse events (AEs) (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)" and "specific AEs" because the analyses based on incidence density ratios presented by the company did not adequately consider the different median observation durations in the study arms of the ASPIRE study (carfilzomib arm: 88 weeks; comparator arm: 57 weeks).

With its comments, the company subsequently submitted the missing data on the questionnaires EORTC QLQ-C30 and QLQ-MY20 as well as survival time analyses on AE outcomes. The survival time analyses on common AEs subsequently submitted were still incomplete, impeding a choice of specific AEs also in the present addendum (see Section 2.1.2).

The data subsequently submitted by the company and the resulting changes regarding risk of bias and assessment of the added benefit are described below.

2.1.1 Risk of bias

In dossier assessment A17-38, the risk of bias of the ASPIRE study was rated as high due to the possible selective reporting. Table 1 shows the risk of bias of the ASPIRE study at study level, resulting from the data subsequently submitted by the company with the comments.

Table 1: Risk of bias at study level – RCT, direct comparison: carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
ASPIRE	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

Based on the data subsequently submitted by the company, selective reporting is no longer assumed; hence, in contrast to the assessment in the dossier assessment, the risk of bias at study level was rated as low.

Limitations resulting from the open-label study design are considered in the outcome-specific risk of bias.

Table 2 shows the risk of bias for the relevant outcomes, resulting from the data subsequently submitted by the company.

Table 2: Risk of bias at study and outcome level – RCT, direct comparison: carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone

Study		Outcomes					
	Study level	Overall survival	Symptoms (symptom scales of EORTC QLQ-C30 and QLQ-MY20)	Health-related quality of life (EORTC QLQ-C30 and QLQ-MY20)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)
ASPIRE	L	L	H[a, b]	H[a, b]	H[c]	H[a]	H[c]

a: Lack of blinding in subjective recording of outcomes.
b: Decreasing response to questionnaires in the course of the study; large proportion of patients not included in the analysis (> 10%) or large difference between the treatment groups (> 5 percentage points).
c: Large difference in median treatment duration (and hence observation period) between the intervention arm (88 weeks) and the control arm (57 weeks).
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; H: high; L: low; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Due to the risk of bias at study level now rated as low, the present addendum also rates the risk of bias of the outcome “overall survival” as low.

The risk of bias for the outcomes on symptoms and health-related quality of life was rated as high due to the lack of blinding in subjective recording of outcomes and high proportions of patients not included in the analyses. Due to the large differences in the median treatment duration and hence observation period, the risk of bias of the outcomes “SAEs” and “severe AEs” was also rated as high. Potential bias of the outcome “discontinuation due to AEs” was caused by the lack of blinding.

Based on the available data and due to the high risk of bias, at most an indication of an added benefit can therefore be derived for the outcome “overall survival” and at most hints for all further outcomes.

2.1.2 Results

Table 3 and Table 4 summarize the data subsequently submitted by the company on the comparison of carfilzomib + lenalidomide + dexamethasone with lenalidomide + dexamethasone. Where necessary, calculations by the Institute are provided in addition to the data. Kaplan-Meier curves on the side effect outcomes can be found in Appendix A.

The company additionally presented the final clinical study report (CSR) from the second data cut-off of the ASPIRE study. All relevant data of this data cut-off in the form of a summarizing version were already available for dossier assessment A17-38, with the exception of common AEs by System Organ Class (SOC). These were additionally provided in the tables on common AEs (see Appendix B). Outcomes on morbidity and health-related quality of life were no longer recorded after the first data cut-off, hence the results of the first data cut-off were also used for these outcomes.

Table 3: Results (morbidity and health-related quality of life) – RCT, direct comparison: carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone, supplementary presentation

Study **Outcome category** **Outcome**	**Carfilzomib + lenalidomide + dexamethasone**		**Lenalidomide + dexamethasone**		**Carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone**
	N	**Median time to event in days [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in days [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value**
Study ASPIRE					
Morbidity (first data cut-off 16 June 2014)					
Symptoms (EORTC QLQ-C30 – time to deterioration ≥ 10 points)					
Fatigue	396	142 [141; 308] 211 (53.3)	396	172 [141; 316] 188 (47.5)	1.05 [0.86; 1.28]; 0.624[a]
Nausea/vomiting	396	639 [494; 639] 108 (27.3)	396	515 [515; NC] 94 (23.7)	0.93 [0.71; 1.23]; 0.630[a]
Pain	396	484 [326; 511] 159 (40.2)	396	481 [331; NC] 140 (35.4)	0.97 [0.77; 1.22]; 0.791[a]
Dyspnoea	396	492 [477; NC] 151 (38.1)[b]	396	520 [449; NC] 131 (33.1)[b]	1.02 [0.80; 1.29]; 0.882[a]
Insomnia	396	477 [310; 489] 167 (42.2)[b]	396	477 [309; 486] 150 (37.9)[b]	0.92 [0.74; 1.15]; 0.460[a]
Appetite loss	396	494 [484; NC] 135 (34.1)[b]	396	NC [492; NC] 94 (23.7)[b]	1.32 [1.01; 1.71]; 0.043[a]
Diarrhoea	396	477 [316; 477] 181 (45.7)[b]	396	477 [323; 489] 136 (34.3)[b]	1.11 [0.89; 1.39]; 0.350[a]
Constipation	396	526 [497; NC] 113 (28.5)[b]	396	484 [318; NC] 139 (35.1)[b]	0.68 [0.53; 0.87]; 0.003[a]
Symptoms (EORTC QLQ-MY20 – time to deterioration ≥ 10 points)					
Disease-related symptoms[c]	396	526 [484; 639] 130 (32.8)	396	499 [479; 520] 122 (30.8)	0.86 [0.67; 1.11]; 0.244[a]
Side effects of treatment[c]	396	478 [319; NC] 157 (39.6)	396	481 [317; 583] 141 (35.6)	1.00 [0.79; 1.25]; 0.975[a]

(continued)

Table 3: Results (morbidity and health-related quality of life) – RCT, direct comparison: carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone, supplementary presentation (continued)

Study Outcome category Outcome	Carfilzomib + lenalidomide + dexamethasone		Lenalidomide + dexamethasone		Carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone
	N	Median time to event in days [95% CI] Patients with event n (%)	N	Median time to event in days [95% CI] Patients with event n (%)	HR [95% CI]; p-value
Study ASPIRE					
Health-related quality of life (first data cut-off 16 June 2014)					
EORTC QLQ-C30 functional scales (time to deterioration by 10 points)					
Global health status	396	498 [477; NC] 144 (36.4)	396	358 [309; NC] 152 (38.4)	0.79 [0.63; 0.99]; 0.039[a]
Physical functioning	396	512 [491; 639] 141 (35.6)	396	477 [316; 491] 146 (36.9)	0.79 [0.63; 1.00]; 0.0503[a]
Role functioning	396	310 [155; 477] 186 (47.0)	396	310 [172; 475] 171 (43.2)	0.96 [0.78; 1.19]; 0.730[a]
Emotional functioning	396	554 [493; NC] 124 (31.3)[b]	396	NC [486; NC] 118 (29.8)[b]	0.90 [0.70; 1.16]; 0.436[a]
Cognitive functioning	396	338 [309; 477] 184 (46.5)[b]	396	316 [184; 477] 162 (40.9)[b]	0.99 [0.80; 1.22]; 0.904[a]
Social functioning	396	477 [309; 499] 171 (43.2)[b]	396	309 [148; 476] 174 (43.9)[b]	0.85 [0.68; 1.04]; 0.119[a]
EORTC QLQ-MY20 (time to deterioration by 10 points)					
Future perspective	396	141 [74; 141] 266 (67.2)[b]	396	141 [139; 148] 216 (54.5)[b]	1.17 [0.98; 1.40]; 0.081[a]
Body image	396	NC [NC; NC] 104 (26.3)[b]	396	570 [570; NC] 100 (25.3)[b]	0.90 [0.69; 1.19]; 0.478[a]

a: 2-sided p-value, calculated using Cox regression, adjusted for pretreatment with bortezomib (yes, no), pretreatment with lenalidomide (yes, no) and beta-2 microglobulin (< 2.5 mg/L, ≥ 2.5 mg/L).
b: Institute's calculation.
c: Allocated to health-related quality of life by the company.

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NC: not calculable; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Table 4: Results (side effects) – RCT, direct comparison: carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone

Study Outcome category Outcome	Carfilzomib + lenalidomide + dexamethasone		Lenalidomide + dexamethasone		Carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][a]; p-value
ASPIRE					
Side effects					
AEs (supplementary information)	392	0.3 [0.1; 0.3] 384 (98.0)	389	0.4 [0.3; 0.5] 381 (97.9)	–
SAEs	392	12.7 [10.1; 16.0] 257 (65.6)	389	15.4 [12.7; 19.1] 221 (56.8)	1.06 [0.89; 1.27]; 0.515[b]
Severe AEs (CTCAE grade ≥ 3)	392	16.9 [13.7; 22.7] 341 (87.0)	389	20.9 [18.7; 27.3] 323 (83.0)	1.11 [0.92; 1.34]; 0.290[b]
Discontinuation due to AEs					
Total study medication	392	ND 75 (19.1)	389	ND 80 (20.6)	RR: 0.93 [0.70; 1.23]; 0.683[c]
≥ 1 study medication	392	ND 131 (33.4)	389	ND 117 (30.1)	RR: 1.11 [0.90; 1.37]; 0.370[c]

a: Unless stated otherwise.
b: 2-sided p-value, calculated using Cox regression, unadjusted.
c: Institute's calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [5]).
AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Mortality

Overall survival

The results on overall survival can be found in dossier assessment A17-38. Under consideration of the data subsequently submitted by the company and the changed assessment of the risk of bias of the ASPIRE study (see Section 2.1.1), there was an indication of an added benefit of carfilzomib + lenalidomide + dexamethasone versus lenalidomide + dexamethasone for the outcome "overall survival" for patients < 65 years.

Morbidity

Symptoms

Symptom outcomes were recorded with the symptom scales of the disease-specific instrument EORTC QLQ-C30 and of the myeloma-specific supplementary tool EORTC QLQ-MY20.

For the outcome **"appetite loss"**, a statistically significant difference to the disadvantage of carfilzomib + lenalidomide + dexamethasone versus lenalidomide + dexamethasone was shown; the extent of the effect in this non-serious/non-severe outcome was no more than marginal, however. This resulted in no hint of an added benefit of carfilzomib + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone for this outcome; an added benefit for this outcome is therefore not proven.

A statistically significant difference in favour of carfilzomib + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone was shown for the outcome **"constipation"**. This resulted in a hint of an added benefit of carfilzomib + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone for this outcome.

No statistically significant difference between carfilzomib + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone was shown for any of the other symptom outcomes. Hence there was no hint of an added benefit of carfilzomib + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone for any further symptom outcome; an added benefit is therefore not proven for any further symptom outcome.

Health-related quality of life

Outcomes on health-related quality of life were recorded with the functional scales of the disease-specific instrument EORTC QLQ-C30 and of the myeloma-specific supplementary tool EORTC QLQ-MY20.

A statistically significant difference in favour of carfilzomib + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone was shown for the outcome **"global health status"**. This resulted in a hint of an added benefit of carfilzomib + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone.

No statistically significant difference between carfilzomib + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone was shown for any of the other outcomes on health-related quality of life. Hence there was no hint of an added benefit of carfilzomib + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone for any further outcome on health-related quality of life; an added benefit is therefore not proven for any further outcome on health-related quality of life.

Side effects

Serious adverse events, severe adverse events (CTCAE grade ≥ 3), discontinuation due to adverse events

No statistically significant differences between the treatment arms were shown for the outcomes "SAEs", "severe AEs (CTCAE grade ≥ 3)" and "discontinuation due to AEs". This resulted in no hint of greater or lesser harm from carfilzomib + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone; greater or lesser harm is therefore not proven for these outcomes.

Specific adverse events

A choice of specific AEs was also not possible in the present addendum. Due to the differences in treatment duration between the study arms, survival time analyses were required for the choice and the interpretation of specific AEs. These were presented only selectively for common SAEs with CTCAE grade ≥ 3 (SOCs and Preferred Terms [PTs]) and common severe AEs (CTCAE grade ≥ 3) (only PTs) in the company's comments. There were no survival time analyses for common SAEs of any severity grade, common severe AE at SOC level, and common AEs in general. Contrary to the company's statement in the oral hearing on carfilzomib [4], frequencies of events, for which a calculation of survival time analyses would have been possible and necessary, were shown for a number of common AEs, SAEs, and severe AEs (see Appendix B).

Subgroups

No relevant effect modifications resulted from the data subsequently submitted by the company on outcomes of morbidity and health-related quality of life.

The company presented no usable subgroup analyses on outcomes on side effects. According to the company's statement in the oral hearing [4], no relevant effect modifications were shown here. This statement could not be verified.

2.1.3 Probability and extent of added benefit

The derivation of probability and extent of the added benefit under consideration of the data subsequently submitted by the company in the commenting procedure is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [6].

2.1.3.1 Assessment of the added benefit at outcome level

Based on the results presented in benefit assessment A17-38 and in Section 2.1.2 of the present addendum, the extent of the respective added benefit is estimated at outcome level (see Table 5).

Table 5: Extent of added benefit at outcome level: carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone** **Median of time to event or proportion of events** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival		
Age		
< 65 years	55.6 vs. 38.2 months HR: 0.68 [0.52; 0.87]; p = 0.003 probability: "indication"	Outcome category: "mortality" $0.85 \leq CI_u < 0.95$ Added benefit, extent: "considerable"
≥ 65 years	36.6 vs. 41.2 months HR: 0.96 [0.76; 1.22]; p = 0.707	Lesser benefit/added benefit not proven
Morbidity		
Symptoms		
EORTC QLQ-C30 (symptom scales) – time to deterioration		
Fatigue	142 vs. 172 days HR: 1.05 [0.86; 1.28]; p = 0.624	Lesser benefit/added benefit not proven
Nausea/vomiting	639 vs. 515 days HR: 0.93 [0.71; 1.23]; p = 0.630	Lesser benefit/added benefit not proven
Pain	484 vs. 481 days HR: 0.97 [0.77; 1.22]; p = 0.791	Lesser benefit/added benefit not proven
Dyspnoea	492 vs. 520 days HR: 1.02 [0.80; 1.29]; p = 0.882	Lesser benefit/added benefit not proven
Insomnia	477 vs. 477 days HR: 0.92 [0.74; 1.15]; p = 0.460	Lesser benefit/added benefit not proven
Appetite loss	494 days vs. NC HR: 1.32 [1.01; 1.71]; p = 0.043 HR: 0.76 [0.58; 0.99][c]	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Lesser benefit/added benefit not proven[d]
Diarrhoea	477 vs. 477 days HR: 1.11 [0.89; 1.39]; p = 0.350	Lesser benefit/added benefit not proven
Constipation	526 vs. 484 days HR: 0.68 [0.53; 0.87]; p = 0.003 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ Added benefit, extent: "minor"

(continued)

Table 5: Extent of added benefit at outcome level: carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone** **Median of time to event or proportion of events** **Effect estimate [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Morbidity		
Symptoms		
EORTC QLQ-MY20 – time to deterioration		
Disease-related symptoms	526 vs. 499 days HR: 0.86 [0.67; 1.11]; p = 0.244	Lesser benefit/added benefit not proven
Side effects of treatment	478 vs. 481 days HR: 1.00 [0.79; 1.25]; p = 0.975	Lesser benefit/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 (functional scales) – time to deterioration		
Global health status	498 vs. 358 days HR: 0.79 [0.63; 0.99]; p = 0.039 Probability: "hint"	Outcome category: serious/severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Added benefit, extent: "minor"
Physical functioning	512 vs. 477 days HR: 0.79 [0.63; 1.00]; p = 0.0503	Lesser benefit/added benefit not proven
Role functioning	310 vs. 310 days HR: 0.96 [0.78; 1.19]; p = 0.730	Lesser benefit/added benefit not proven
Emotional functioning	554 days vs. NC HR: 0.90 [0.70; 1.16]; p = 0.436	Lesser benefit/added benefit not proven
Cognitive functioning	338 vs. 316 days HR: 0.99 [0.80; 1.22]; p = 0.904	Lesser benefit/added benefit not proven
Social functioning	477 vs. 309 days HR: 0.85 [0.68; 1.04]; p = 0.119	Lesser benefit/added benefit not proven
EORTC QLQ-MY20 – time to deterioration		
Future perspective	141 vs. 141 days HR: 1.17 [0.98; 1.40]; p = 0.081	Lesser benefit/added benefit not proven
Body image	NC vs. 570 days HR: 0.90 [0.69; 1.19]; p = 0.478	Lesser benefit/added benefit not proven

(continued)

Table 5: Extent of added benefit at outcome level: carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone** **Median of time to event or proportion of events** **Effect estimate [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Side effects		
SAEs	12.7 vs. 15.4 months HR: 1.06 [0.89; 1.27]; p = 0.515	Greater/lesser harm not proven
Severe AEs (CTCAE grade ≥ 3)	16.9 vs. 20.9 months HR: 1.11 [0.92; 1.34]; p = 0.290	Greater/lesser harm not proven
Discontinuation due to AEs		
Total study medication	Proportion of events: 19.1% vs. 20.6% RR: 0.93 [0.70; 1.23]; p = 0.683	Greater/lesser harm not proven
≥ 1 study medication	Proportion of events: 33.4% vs. 30.1% RR: 1.11 [0.90; 1.37]; p = 0.370	

a: Probability provided if a statistically significant and relevant effect is present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
d: The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20; RR: relative risk; SAE: serious adverse event; vs.: versus

2.1.3.2 Overall conclusion on added benefit

Table 6 summarizes the results considered in the overall conclusion on extent of added benefit.

Table 6: Positive and negative effects from the assessment of carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone

Positive effects	**Negative effects**
Mortality ▪ Overall survival: ▫ age (< 65 years): indication of an added benefit – extent: “considerable”	–
Health-related quality of life ▪ global health status: hint of an added benefit – extent: “minor”	–
Non-serious/non-severe symptoms/late complications ▪ constipation: hint of an added benefit – extent “minor”	
There were no usable data for specific AEs.	
AE: adverse event; vs.: versus	

Overall, there were only positive effects for carfilzomib + lenalidomide + dexamethasone. These were shown in the outcome categories of mortality and health-related quality of life, and non-serious/non-severe symptoms, partly for individual subgroups. No conclusions could be drawn for specific AEs because no usable data were available.

In the overall consideration, there is an indication of a considerable added benefit for patients < 65 years of age. For patients ≥ 65 years, there is a hint of a minor added benefit.

2.1.4 List of included studies

ASPIRE

Reference on the ASPIRE study subsequently submitted by the company with the comments:

Amgen. A Randomized, Multicenter, Phase 3 Study Comparing Carfilzomib, Lenalidomide, and Dexamethasone (CRd) vs Lenalidomide and Dexamethasone (Rd) in Subjects With Relapsed Multiple Myeloma; study ASPIRE; Clinical Study Report [unpublished]. 2017.

Further references of the ASPIRE study can be found in dossier assessment A17-38 [1].

2.2 Assessment of the ENDEAVOR study

Research question

Besides the ASPIRE study, the company presented in its dossier the results of the ENDEAVOR study on the combination of carfilzomib with dexamethasone for the assessment of the added benefit of carfilzomib in patients with multiple myeloma who have received at least one prior therapy. Hence the ENDEAVOR study principally investigates the same patient population as the ASPIRE study. Nonetheless, a joint consideration of both studies is not meaningfully possible due to the different design of the studies. The ASPIRE study investigates carfilzomib as add-on therapy to treatment with lenalidomide + dexamethasone, whereas the ENDEAVOR study conducts a direct comparison of carfilzomib versus bortezomib (each in combination with dexamethasone).

The results of the ENDEAVOR study are described below.

Study characteristics

The ENDEAVOR study is an ongoing, open-label RCT on the comparison of carfilzomib + dexamethasone with bortezomib + dexamethasone in adult patients with relapsed or progressive multiple myeloma who have received at least one and at most 3 prior therapies.

According to the Summary of Product Characteristics (SPC), bortezomib is approved for patients with multiple myeloma who have received at least one prior therapy and who have already undergone or are unsuitable for haematopoietic stem cell transplantation [7]. Approximately 42% of the patients included in the ENDEAVOR study had not yet received stem cell transplantation; it was not clear from the study documents whether and how many of these patients were actually unsuitable for stem cell transplantation. Detailed reasons can be found in dossier assessment A17-38 [1].

As a result of the written comments [3] and the discussion in the oral hearing [4], however, the inclusion criteria of the ENDEAVOR study were considered adequate and in line with the German health care context. The results of the ENDEAVOR study are described and assessed below.

Information on the characteristics of the study and of the interventions of the ENDEAVOR study can be found in dossier assessment A17-38 [1].

Analysis and data cut-offs

Analyses on 2 data cut-offs were available for the ENDEAVOR study:

- first data cut-off (10 November 2014): prespecified analysis for progression-free survival (PFS) conducted on the presence of 414 events
- second data cut-off (3 January 2017): prespecified analysis for overall survival conducted on the presence of 80% of the planned 496 deaths

For the present benefit assessment, analyses on both data cut-offs were available for the outcome categories "mortality" and "side effects". The data of the most recent data cut-off were used for these outcomes for the benefit assessment. For the outcomes on morbidity and health-related quality of life, only results of the first data cut-off from 10 November 2014 were available. Since, according to the information provided in the CSR, no further recording of the questionnaire on morbidity and health-related quality of life was to be conducted after the first data cut-off, the results on the first data cut-off were used for these outcomes.

Planned duration of follow-up observation

Table 7 shows the planned duration of follow-up observation of the patients for the individual outcomes.

Table 7: Planned duration of follow-up observation – RCT, direct comparison: carfilzomib + dexamethasone vs. bortezomib + dexamethasone

Study **Outcome category** **Outcome**	**Planned follow-up observation**
ENDEAVOR	
Mortality	
Overall survival	After treatment discontinuation: every 3 months until death, end of study, or withdrawal of consent
Morbidity	
Symptoms (symptom scales of the EORTC QLQ-C30 and QLQ-MY20) and neurotoxicity (FACT/GOG-Ntx)	In case of treatment discontinuation before progression: every 4 weeks until progression, withdrawal of consent, or start of further myeloma therapy; otherwise only until treatment discontinuation
Health-related quality of life	
Functional scales of the EORTC QLQ-C30 and the QLQ-MY20	In case of treatment discontinuation before progression: every 4 weeks until progression, withdrawal of consent, or start of further myeloma therapy; otherwise only until treatment discontinuation
Side effects	Until 30 days after the last dose of the study medication

AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; FACT/GOG-Ntx: Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (subscale); QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Follow-up for the outcome "overall survival" is planned until death, end of study, or withdrawal of consent. The observation periods for the outcomes "morbidity", "health-related quality of life" and "side effects" were systematically shortened because they were only recorded for the period of treatment with the study medication (plus 30 days for side effects) or until the start of a new myeloma treatment (or until progression). To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to record these outcomes over the total period of time, as was the case for survival.

Characteristics of the study population

Table 8 shows the characteristics of the patients in the ENDEAVOR study.

Table 8: Characteristics of the study population – RCT, direct comparison: carfilzomib + dexamethasone vs. bortezomib + dexamethasone

Study Characteristics Category	Carfilzomib + dexamethasone	Bortezomib + dexamethasone
Study ENDEAVOR	N[a] = 464	N[a] = 465
Age [years], mean (SD)	65 (10)	65 (10)
Sex [F/M], %	48/52	51/49
Ethnic origin, n (%)		
White	348 (75.0)	353 (75.9)
Non-white	8 (1.7)	9 (1.9)
Asian	56 (12.1)	57 (12.3)
Other	2 (0.4)[b]	1 (0.2)[c]
Not reported	50 (10.8)	45 (9.7)
ECOG PS, n (%)		
0	221 (47.6)	232 (49.9)
1	211 (45.5)	203 (43.7)
2	32 (6.9)	30 (6.5)
Type of myeloma, n (%)		
IgG	286 (61.6)	284 (61.1)
IgA	90 (19.4)	105 (22.6)
IgD	6 (1.3)	4 (0.9)
Unknown	82 (17.7)	72 (15.5)
ISS stage at study start, n (%)		
I	212 (45.7)	205 (44.1)
II	138 (29.7)	151 (32.5)
III	114 (24.6)	109 (23.4)
Disease duration: time between first diagnosis and randomization [months], median [min; max]	44.3 [4.0; 246.6]	43.3 [5.4; 306.2]
Prior therapies[d]		
Systemic treatment	464 (100.0)	465 (100.0)
Stem cell therapy	266 (57.3)	272 (58.5)
Radiation	117 (25.2)	103 (22.2)
Bortezomib	250 (53.7)	252 (54.2)
IMiD[e]	325 (70.0)	348 (74.8)
Number of prior therapies		
1	232 (50.0)	232 (49.9)
2	157 (33.8)	145 (31.2)
3	75 (16.2)	87 (18.7)
4	0 (0.0)	1 (0.2)

(continued)

Table 8: Characteristics of the study population – RCT, direct comparison: carfilzomib + dexamethasone vs. bortezomib + dexamethasone (continued)

Study Characteristics Category	Carfilzomib + dexamethasone	Bortezomib + dexamethasone
Study ENDEAVOR	N[a] = 464	N[a] = 465
Choice of bortezomib administration in the study[f]		
Intravenous	108 (23.3)	108 (23.2)
Subcutaneous	356 (76.7)	357 (76.8)
Treatment discontinuation, n (%)	263 (56.7)	351 (75.5)
Study discontinuation, n (%)	ND	ND

a: Number of randomized patients.
b: „Native Hawaiian/other Pacific Islander“ selected.
c: „Multiple“ selected.
d: Multiple answers possible.
e: Institute’s calculation.
f: The type of bortezomib administration (in case that the patient was randomized to the comparator arm) was chosen before randomization.
ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; IgX: immunoglobulin X; IMiD: immunomodulatory drug; ISS: International Staging System; M: male; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The patient characteristics were largely comparable between the treatment groups of the ENDEAVOR study. Most patients were white; the mean age was 65 years. According to the inclusion criteria, all patients had received at least one systemic treatment for multiple myeloma before study inclusion. About half of the patients were pretreated with 2 or more therapies. The majority of the patients included were allocated to International Staging System (ISS) stage I or II and had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1. About 60% of the patients had received prior autologous stem cell transplantation.

Course of the study

Table 9 shows the median treatment duration of the patients and the median observation period for individual outcomes.

Table 9: Information on the course of the study – RCT, direct comparison: carfilzomib + dexamethasone vs. bortezomib + dexamethasone

Study **Duration of the study phase** **Outcome category** **Study medication**	**Carfilzomib + dexamethasone**	**Bortezomib + dexamethasone**
Study ENDEAVOR	N = 463	N = 456
Treatment duration [weeks]		
Data cut-off: 10 November 2014		
Carfilzomib, median [min; max]	39.9 [1.0; 108.1]	–
Bortezomib, median [min; max]	–	26.8 [1.0; 106.1]
Dexamethasone, median [min; max]	39.0 [1.0; 108.1]	26.0 [1.0; 106.1]
Data cut-off: 3 January 2017		
Carfilzomib, median [min; max]	48.0 [1.0; 213.0]	–
Bortezomib, median [min; max]	–	27.0 [1.0; 198.1]
Dexamethasone, median [min; max]	45.9 [1.0; 212.0]	26.9 [1.0; 198.1]
Observation period [weeks]		
Overall survival, median [95% CI][a]		
Data cut-off 10 November 2014	54.1 [51.5; 57.2][c]	51.5 [48.5; 54.6][c]
Data cut-off 3 January 2017	162.4 [159.3; 165.8][c]	159.8 [156.7; 162.8][c]
Morbidity[b], health-related quality of life[b], side effects	ND	ND

a: ITT population: N = 464 in the intervention arm, and N = 465 in the comparator arm.
b: Recorded with the questionnaires EORTC QLQ-C30, EORTC QLQ-MY20, and FACT/GOG-Ntx.
c: Institute's calculation from data in months.

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; FACT/GOG-Ntx: Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity; ITT: intention to treat; max: maximum; min: minimum; N: number of patients who have received at least one study medication (safety population); ND: no data; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20; RCT: randomized controlled trial; vs.: versus

The differences in median treatment duration shown at the first data cut-off from 10 November 2014 (39.9 versus 26.8 weeks for carfilzomib or bortezomib) increased until the second data cut-off from 3 January 2017 and were 48.0 weeks in the carfilzomib arm versus 27.0 weeks in the comparator arm.

The median observation period for the outcome "overall survival" in the study arms was about the same at both data cut-offs. No information on the observation period was available for the outcomes of the categories "morbidity", "health-related quality of life" and "side effects". Due to the planned duration of the follow-up observation (see Table 7) and the differences in treatment duration and the time to progression, it can be assumed that there was a relevant difference in the observation periods for these outcomes between the study arms, however.

Applicability of the results

As described in the dossier assessment, in contrast to the approval of bortezomib, continuation of treatment with bortezomib + dexamethasone beyond 8 cycles was possible in the comparator arm of the ENDEAVOR study. According to the SPC [8], pretreated patients achieving a response or a stable disease after 4 cycles of therapy with bortezomib + dexamethasone can continue to receive the same combination for a maximum of 4 additional cycles.

No information was provided on efficacy and safety of such prolonged bortezomib administration. The applicability of the results of the ENDEAVOR study to the research question of the benefit assessment is therefore unclear.

Risk of bias at study level

Table 10 shows the risk of bias at study level.

Table 10: Risk of bias at study level – RCT, direct comparison: carfilzomib + bortezomib + dexamethasone vs. bortezomib + dexamethasone

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
ENDEAVOR	Yes	No	No	No	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level for the ENDEAVOR study was rated as low.

Limitations resulting from the open-label study design are described with the outcome-specific risk of bias in Section 2.2.1.2.

2.2.1 Results on added benefit

2.2.1.1 Outcomes included

The following patient-relevant outcomes were to be considered in the assessment:

- Mortality
  - overall survival
- Morbidity
  - symptoms measured with the symptom scales of the instruments EORTC QLQ-C30 and EORTC QLQ-MY20
  - neurotoxicity measured with the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx)
- Health-related quality of life
  - measured with the functional scales of the EORTC QLQ-C30 and of the EORTC QLQ-MY20
- Side effects
  - SAES
  - discontinuation due to AEs
  - severe AEs (CTCAE grade ≥ 3)
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A).

The outcomes “PFS”, “time to initiation of subsequent therapy”, “response”, and “duration of remission” in the present operationalization were not considered to be patient-relevant outcomes and were therefore not used for the benefit assessment. A detailed explanation can be found in dossier assessment A17-38. The AE outcome “neuropathy peripheral” was not used for the present benefit assessment because no usable data were available on further specific AEs (see Section 2.2.1.3), and hence a comprehensive assessment of specific AEs was not possible. The results on this outcome (for CTCAE grade ≥ 3) are presented in Table 26 together with the common severe AEs.

Table 11 shows for which outcomes data were available in the study included.

Table 11: Matrix of outcomes – RCT, direct comparison: carfilzomib + dexamethasone vs. bortezomib + dexamethasone

Study	Outcomes						
ENDEAVOR	**Overall survival**	**Symptoms (symptom scales EORTC QLQ-C30 and QLQ-MY20)**	**Neurotoxicity (FACT/GOG-Ntx)**	**Health-related quality of life (EORTC QLQ-C30 and QLQ-MY20)**	**SAEs**	**Discontinuation due to AEs**	**Severe AEs (CTCAE grade ≥ 3)**
Data cut-off 10 Nov 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Data cut-off 3 Jan 2017	Yes	No	No	No	Yes	Yes	Yes

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; FACT/GOG-Ntx: Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (subscale); QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

The most recent data for the individual outcomes were used for the present assessment (see also Section “Analysis and data cut-offs”).

2.2.1.2 Risk of bias

Table 12 describes the risk of bias for the relevant outcomes.

Table 12: Risk of bias at study and outcome level – RCT, direct comparison: carfilzomib + dexamethasone vs. bortezomib + dexamethasone

Study	Study level	Outcomes						
		Overall survival	Symptoms (symptom scales EORTC QLQ-C30 and QLQ-MY20)	Health-related quality of life (EORTC QLQ-C30 and QLQ-MY20)	Neurotoxicity (FACT/GOG-Ntx)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)
ENDEAVOR	L	L	H[a, b]	H[a, b]	H[a, b]	H[c]	H[a]	H[c]

a: Lack of blinding in subjective recording of outcomes.
b: Decreasing response to questionnaires in the course of the study; large proportion of patients not included in the analysis (> 10%) or large difference between the treatment groups (> 5 percentage points); different intervals from the end of a treatment cycle and the recording of outcomes between the treatment groups
c: Large difference in median treatment duration (and hence observation period) between the intervention arm (48 weeks) and the control arm (27 weeks).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; FACT/GOG-Ntx: Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity; H: high; L: low; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

The risk of bias for the outcome "overall survival" was rated as low.

The risk of bias for the outcomes on morbidity, symptoms and health-related quality of life was rated as high due to the lack of blinding and high proportions of patients not included in the analyses. The fact that the questionnaires on patient-reported outcomes (EORTC QLQ-C30, QLQ-MY20, and FACT/GOG-Ntx) were recorded every 28 days in both treatment arms also contributed to the high risk of bias. Since treatment in the intervention arm was conducted in 28-day cycles, the recording of the questionnaires was conducted at the start of each new cycle. In the comparator arm, in contrast, treatment was in 21-day cycles; hence the recording of the questionnaires in the comparator arm was conducted at different time points within the cycles.

Due to the large differences in the median treatment duration and hence observation period, the risk of bias of the outcomes "SAEs" and "severe AEs" was also rated as high. Potential bias of the outcome "discontinuation due to AEs" was caused by the lack of blinding.

2.2.1.3 Results

Table 13, Table 14 and Table 15 summarize the results of the comparison of carfilzomib + dexamethasone versus bortezomib + dexamethasone in adults with multiple myeloma who have received at least one prior therapy. Where necessary, Institute's own calculations are provided in addition to the data from the company's dossier. Kaplan-Meier curves on overall survival and on the side effect outcomes can be found in Appendix C. Results on common AEs are presented in Appendix D.

Table 13: Results (mortality, morbidity and health-related quality of life) – RCT, direct comparison: carfilzomib + dexamethasone vs. bortezomib + dexamethasone

Study Outcome category Outcome	Carfilzomib + dexamethasone		Bortezomib + dexamethasone		Carfilzomib + dexamethasone vs. bortezomib + dexamethasone
	N	Median time to event [95% CI] Patients with event n (%)	N	Median time to event [95% CI] Patients with event n (%)	HR [95% CI][a]; p-value
ENDEAVOR					
Mortality (data cut-off 3 January 2017)					
Overall survival [in months]	464	47.6 [42.5; NA] 189 (40.7)	465	40.0 [32.6; 42.3] 209 (44.9)	0.791 [0.648; 0.964]; 0.020[b]
Morbidity (data cut-off 10 November 2014)					
Symptoms (EORTC QLQ-C30, time to deterioration ≥ 10 points [in days])					
Fatigue	464	57 [57; 59] 301 (64.9)	465	57 [53; 79] 280 (60.2)	0.90 [0.76; 1.06]; 0.199
Nausea/vomiting	464	537 [337; NA] 153 (33.0)	465	251 [197; 361] 152 (32.7)	0.78 [0.62; 0.98]; 0.036
Pain	464	169 [141; 213] 227 (48.9)	465	121 [106; 168] 210 (45.2)	0.86 [0.72; 1.04]; 0.128
Dyspnoea	464	86 [85; 113] 271 (58.4[c])	465	113 [86; 148] 215 (46.2[c])	1.11 [0.93; 1.33]; 0.242
Insomnia	464	111 [84; 141] 244 (52.6[c])	465	85 [57; 105] 240 (51.6[c])	0.80 [0.67; 0.95]; 0.013
Appetite loss	464	337 [281; NA] 172 (37.1[c])	465	166 [137; 207] 191 (41.1[c])	0.66 [0.54; 0.81]; < 0.001
Diarrhoea	464	309 [253; 453] 178 (38.4[c])	465	169 [141; 225] 184 (39.6[c])	0.71 [0.58; 0.88]; 0.001
Constipation	464	NA [456; NA] 129 (27.8[c])	465	141 [109; 220] 190 (40.9[c])	0.47 [0.38; 0.59]; < 0.001
Symptoms (EORTC QLQ-MY20, time to deterioration ≥ 10 points [in days])					
Disease-related symptoms[d]	464	393 [256; NA] 168 (36.2)	465	250 [196; 651] 155 (33.3)	0.88 [0.71; 1.10]; 0.271
Side effects of treatment[d]	464	196 [141; 251] 218 (47.0)	465	113 [89; 116] 235 (50.5)	0.65 [0.54; 0.78]; < 0.001

(continued)

Table 13: Results (mortality, morbidity and health-related quality of life) – RCT, direct comparison: carfilzomib + dexamethasone vs. bortezomib + dexamethasone (continued)

Study Outcome category Outcome	Carfilzomib + dexamethasone		Bortezomib + dexamethasone		Carfilzomib + dexamethasone vs. bortezomib + dexamethasone
	N	Median time to event [95% CI] Patients with event n (%)	N	Median time to event [95% CI] Patients with event n (%)	HR [95% CI][a]; p-value
ENDEAVOR					
Health-related quality of life (data cut-off 10 November 2014)					
EORTC QLQ-C30 functional scales (time to deterioration by 10 points [in days])					
Global health status	464	113 [86.0; 141] 244 (52.6)	465	85 [85; 106] 248 (53.3)	0.77 [0.65; 0.92]; 0.005
Physical functioning	464	169 [141; 225] 221 (47.6)	465	114 [99; 168] 214 (46.0)	0.82 [0.68; 0.99]; 0.039
Role functioning	464	85 [58; 88] 280 (60.3[c])	465	85 [66; 99] 254 (54.6[c])	0.95 [0.80; 1.13]; 0.558
Emotional functioning	464	211 [169; 337] 207 (44.6[c])	465	193 [141; 225] 184 (39.6[c])	0.86 [0.70; 1.05]; 0.138
Cognitive functioning	464	142 [114; 197] 234 (50.4[c])	465	113 [87; 147] 215 (46.2[c])	0.83 [0.69; 1.00]; 0.046
Social functioning	464	85 [85; 113] 258 (55.6[c])	465	85 [84; 112] 254 (54.6[c])	0.84 [0.70; 1.00]; 0.046
EORTC QLQ-MY20 (time to deterioration by 10 points [in days])					
Future perspective	464	56 [30; 57] 313 (67.5[c])	465	50 [36; 56] 261 (56.1[c])	1.01 [0.86; 1.19]; 0.916
Body image	464	NA [NA; NA] 127 (27.3[c])	465	NA [NA; NA] 92 (19.8[c])	1.20 [0.92; 1.58]; 0.176

a: 2-sided p-value, calculated using Cox regression, adjusted for pretreatment with proteasome inhibitor (yes, no), number of prior therapies (1, 2 or 3 lines of therapy), ISS stage (1, 2 or 3), type of bortezomib administration (IV, SC).
b: Doubling the one-sided p-value of the stratified log-rank test.
c: Institute's calculation.
d: Allocated to health-related quality of life by the company.

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; ISS: International Staging System; IV: intravenous; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20; RCT: randomized controlled trial; RR: relative risk; SC: subcutaneous; vs.: versus

Table 14: Results (side effects) – RCT, direct comparison: carfilzomib + dexamethasone vs. bortezomib + dexamethasone

Study Outcome category Outcome	Carfilzomib + dexamethasone		Bortezomib + dexamethasone		Carfilzomib + dexamethasone vs. bortezomib + dexamethasone
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][a]; p-value
Side effects (data cut-off 3 January 2017)					
AEs (supplementary information)	463	0.1 [0.1; 0.2] 457 (98.7)	456	0.2 [0.2; 0.3] 451 (98.9)	–
SAEs	463	10.9 [8.8; 14.3] 273 (59.0)	456	16.4 [13.8; 22.7] 182 (39.9)	1.22 [1.01; 1.47]; 0.040[b]
Severe AEs (CTCAE grade ≥ 3)	463	3.1 [2.3; 4.0] 377 (81.4)	456	2.9 [2.4; 3.8] 324 (71.1)	1.06 [0.92; 1.24]; 0.413[b]
Discontinuation due to AEs					
≥ 1 study medication	463	33.1 [23.1; NA] 133 (28.7)	456	NA [33.9; NA] 118 (25.9)	RR: 1.11 [0.90; 1.37]; 0.530[c]
Total study medication	463	NA [31.7; NA] 116 (25.1)	456	NA [35.5; NA] 99 (21.7)	RR: 1.15 [0.91; 1.46]; 0.248[c]

a: Unless stated otherwise.
b: 2-sided p-value, calculated using Cox regression, unadjusted.
c: Institute‘s calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [5]).

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Table 15: Results (morbidity, continuous) – RCT, direct comparison: carfilzomib + dexamethasone vs. bortezomib + dexamethasone

Study Outcome category Outcome	Carfilzomib + dexamethasone			Bortezomib + dexamethasone			Carfilzomib + dexamethasone vs. bortezomib + dexamethasone
	N[a]	Values at study start mean (SD)	LSME[b] (SD)	N[a]	Values at study start mean (SD)	LSME[b] (SD)	LSMD[b] [95% CI]; p-value
ENDEAVOR							
FACT/GOG-Ntx (data cut-off 10 November 2014)							
Neurotoxicity	459	37.0 (6.0)	36.0 (ND)	452	37.0 (6.3)	35.2 (ND)	0.84 [0.40; 1.28]; < 0.001 Hedges' g: 0.25 [0.12; 0.38][c]

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: From a mixed-effects model repeated measures (MMRM).
c: Institute's calculation based on the LSMD and the standard error from the MMRM.
CI: confidence interval; FACT/GOG-Ntx: Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (subscale); LSMD: least squares mean difference; LSME: least squares mean estimate; MMRM: mixed-effects model repeated measures; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Based on the available data, at most indications of an added benefit can be derived for the outcome "overall survival". Due to the high risk of bias, at most hints, e.g. of an added benefit, can be determined for all other outcomes.

Mortality

Overall survival

A statistically significant difference in favour of carfilzomib + dexamethasone in comparison with bortezomib + dexamethasone was shown for the outcome "overall survival". This resulted in an indication of an added benefit of carfilzomib + dexamethasone in comparison with bortezomib + dexamethasone.

Morbidity

Symptoms

Symptom outcomes were recorded with the symptom scales of the disease-specific instrument EORTC QLQ-C30 and of the myeloma-specific supplementary tool EORTC QLQ-MY20.

For the outcome **"insomnia"**, a statistically significant difference in favour of carfilzomib + dexamethasone versus bortezomib + dexamethasone was shown; the extent of the effect in this non-serious/non-severe outcome was no more than marginal, however. This resulted in no hint of an added benefit of carfilzomib + dexamethasone in comparison with bortezomib + dexamethasone for this outcome; an added benefit for this outcome is therefore not proven.

No statistically significant difference between the treatment groups was shown for each of the outcomes **"fatigue", "pain", "dyspnoea"** and **"disease-related symptoms"**. This resulted in no hint of an added benefit of carfilzomib + dexamethasone in comparison with bortezomib + dexamethasone; an added benefit for these outcomes is therefore not proven.

Statistically significant differences in favour of carfilzomib + dexamethasone in comparison with bortezomib + dexamethasone were shown for the outcomes **"appetite loss", "diarrhoea"** and **"constipation"**. This resulted in a hint of an added benefit of carfilzomib + dexamethasone in comparison with bortezomib + dexamethasone for each of these outcomes.

A statistically significant difference in favour of carfilzomib + dexamethasone in comparison with bortezomib + dexamethasone was shown for each of the outcomes **"nausea/vomiting"** and **"side effects of treatment"**. In addition, there was an effect modification by the characteristic "prior bortezomib therapy" for these outcomes (see Section 2.2.1.4). For patients with prior bortezomib therapy, there was no hint of an added benefit of carfilzomib + dexamethasone in comparison with bortezomib + dexamethasone; an added benefit is therefore not proven. For patients without prior bortezomib therapy, however, there was a hint of an added benefit of carfilzomib + dexamethasone versus bortezomib + dexamethasone. It must be considered for the outcome **"side effects of treatment"** that the effect only reflects the side effects recorded using the EORTC QLQ-MY20. However, the development of the scale for the recording of side effects of treatment was based on chemotherapies. It cannot be assumed that the scale provides a comprehensive reflection of all side effects of the treatments investigated in the ENDEAVOR study. Since no usable data on specific AEs were available in the present assessment, further interpretation of this outcome is not possible.

Neurotoxicity (FACT/GOG-Ntx)

In the ENDEAVOR study, the outcome "neurotoxicity" was recorded using the FACT/GOG-Ntx questionnaire. In Module 4 A, the company presented analyses on the time to deterioration by a minimally important difference (MID) of 5 points. Since no sufficient information was available on the validity of this MID, the continuous analyses (mixed-effects model repeated measures [MMRM] analyses) available in the CSR were used for the assessment of this outcome.

A statistically significant difference in favour of carfilzomib + dexamethasone in comparison with bortezomib + dexamethasone was shown. However, the confidence interval of Hedges' g was not fully outside the irrelevance range [−0.2; 0.2]; it can therefore not be inferred that the effect is clinically relevant. This resulted in no hint of an added benefit of carfilzomib + dexamethasone in comparison with bortezomib + dexamethasone for this outcome; an added benefit is not proven.

Health-related quality of life

Outcomes on health-related quality of life were recorded with the functional scales of the disease-specific instrument EORTC QLQ-C30 and of the myeloma-specific supplementary tool EORTC QLQ-MY20.

There was a statistically significant effect in favour of carfilzomib + dexamethasone in comparison with bortezomib + dexamethasone for each of the outcomes **"global health status"** and **"cognitive functioning"**. In addition, there was an effect modification by the characteristic "prior bortezomib therapy" for these outcomes (see Section 2.2.1.4). For patients with prior bortezomib therapy, there was no hint of an added benefit of carfilzomib + dexamethasone in comparison with bortezomib + dexamethasone; an added benefit is therefore not proven. For patients without prior bortezomib therapy, however, there was a hint of an added benefit of carfilzomib + dexamethasone versus bortezomib + dexamethasone.

A statistically significant effect in favour of carfilzomib + dexamethasone in comparison with bortezomib + dexamethasone was shown for the outcome **"physical functioning"**. In addition, there was an effect modification by the characteristic "age" for this outcome (see Section 2.2.1.4). For patients ≤ 65 years of age, there was no hint of an added benefit of carfilzomib + dexamethasone in comparison with bortezomib + dexamethasone; an added benefit is therefore not proven. For patients > 65 years of age, however, there was a hint of an added benefit of carfilzomib + dexamethasone versus bortezomib + dexamethasone.

There was no statistically significant effect between the treatment groups for the outcome **"role functioning"**. However, there was an effect modification by the characteristic "age" for this outcome (see Section 2.2.1.4). For patients ≤ 65 years of age, there was no hint of an added benefit of carfilzomib + dexamethasone in comparison with bortezomib + dexamethasone; an added benefit is therefore not proven. For patients > 65 years of age, however, there was a hint of an added benefit of carfilzomib + dexamethasone versus bortezomib + dexamethasone.

A statistically significant effect in favour of carfilzomib + dexamethasone in comparison with bortezomib + dexamethasone was shown for the outcome **"social functioning"**. This resulted in a hint of an added benefit of carfilzomib + dexamethasone in comparison with bortezomib + dexamethasone for this outcome.

There were no statistically significant differences between the treatment groups for the outcomes **"emotional functioning", "future perspective"** and **"body image"**. This resulted in no hint of an added benefit of carfilzomib + dexamethasone in comparison with bortezomib + dexamethasone for these outcomes; an added benefit for these outcomes is therefore not proven.

Side effects

Serious adverse events

A statistically significant difference to the disadvantage of carfilzomib + dexamethasone in comparison with bortezomib + dexamethasone was shown for the outcome "SAEs". This

resulted in a hint of greater harm of carfilzomib + dexamethasone in comparison with bortezomib + dexamethasone.

Severe adverse events (CTCAE grade ≥ 3), discontinuation due to adverse events

No statistically significant differences between the treatment arms were shown for the outcomes "severe AEs (CTCAE grade ≥ 3)" and "discontinuation due to AEs". This resulted in no hint of greater or lesser harm from carfilzomib + dexamethasone in comparison with bortezomib + dexamethasone; greater or lesser harm is therefore not proven for these outcomes.

Specific adverse events

A choice of specific AEs was also not possible in the present addendum. Due to the differences in treatment duration between the study arms, survival time analyses were required for the choice and the interpretation of specific AEs. These were presented only selectively for SAEs with CTCAE grade ≥ 3 (SOCs and PTs) and severe AEs (CTCAE grade ≥ 3) (only PTs) in the company's comments. There were no survival time analyses for overall SAEs, severe AE at SOC level, and AEs in general. Contrary to the company's statement in the oral hearing on carfilzomib [4], frequencies of events, for which a calculation of survival time analyses would have been possible and necessary, were shown for a number of common AEs, SAEs, and severe AEs (see Appendix D).

2.2.1.4 Subgroups and other effect modifiers

Analogous to dossier assessment A17-38 and under consideration of the available data, the following subgroup characteristics were used in the benefit assessment:

- age (< 65 years, ≥ 65 years for overall survival; ≤ 65 years, > 65 years for morbidity and health-related quality of life)
- sex (men, women)
- ethnicity (white, non-white, Asian, other)
- ISS disease stage (I, II or III)
- number of prior therapies (1, 2 or 3)
- prior bortezomib therapy (yes, no)
- prior lenalidomide therapy (yes, no)

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

The company presented no usable subgroup analyses on outcomes on side effects. According to the company's statement in the oral hearing, no relevant effect modifications were shown here. This statement could not be verified.

Table 16 summarizes the subgroup results on the comparison of carfilzomib + dexamethasone with bortezomib + dexamethasone in the ENDEAVOR study.

Table 16: Subgroups (time to event) – RCT, direct comparison: carfilzomib + dexamethasone vs. bortezomib + dexamethasone

Study Outcome Characteristic Subgroup	Carfilzomib + dexamethasone		Bortezomib + dexamethasone		Carfilzomib + dexamethasone vs. bortezomib + dexamethasone	
	N	Median time to event in days [95% CI] Patients with event n (%)	N	Median time to event in days [95% CI] Patients with event n (%)	HR [95% CI]	p-value
ENDEAVOR						
Morbidity (data cut-off 10 November 2014)						
Symptoms (EORTC QLQ-C30 – time to deterioration ≥ 10 points)						
Nausea/vomiting						
Number of prior therapies						
1	231	NA [399; NA] 63 (27.3)	229	251 [170; NA] 74 (32.3)	0.60 [0.43; 0.84]	0.003
2 or 3	233	258 [169; 537] 90 (38.6)	236	280 [194; 421] 78 (33.1)	0.97 [0.71; 1.32]	0.842
Total					Interaction:	0.024
Pretreatment with bortezomib						
Yes	250	399 [253; NA] 86 (34.4)	252	284 [232; 450] 76 (30.2)	0.96 [0.70; 1.31]	0.781
No	214	NA [337; NA] 67 (31.3)	213	197 [144; NA] 76 (35.7)	0.61 [0.44; 0.85]	0.003
Total					Interaction:	0.034
Symptoms (EORTC QLQ-MY20 – time to deterioration ≥ 10 points)						
Side effects of treatment						
Pretreatment with bortezomib						
Yes	250	195 [124; 253] 115 (46.0)	252	120 [107; 173] 111 (44.0)	0.82 [0.63; 1.06]	0.127
No	214	196 [140; 281] 103 (48.1)	213	86 [63; 113] 124 (58.2)	0.52 [0.40; 0.68]	< 0.001
Total					Interaction:	0.048

(continued)

Table 16: Subgroups (time to event) – RCT, direct comparison: carfilzomib + dexamethasone vs. bortezomib + dexamethasone (continued)

Study Outcome Characteristic Subgroup	Carfilzomib + dexamethasone		Bortezomib + dexamethasone		Carfilzomib + dexamethasone vs. bortezomib + dexamethasone	
	N	Median time to event in days [95% CI] Patients with event n (%)	N	Median time to event in days [95% CI] Patients with event n (%)	HR [95% CI]	p-value
Health-related quality of life (data cut-off 10 November 2014)						
EORTC QLQ-C30 functional scales, time to deterioration by ≥ 10 points						
Global health status						
Pretreatment with bortezomib						
Yes	250	88 [85; 140] 138 (55.2)	252	106 [85; 120] 127 (50.4)	0.92 [0.72; 1.17]	0.465
No	214	141 [113; 226] 106 (49.5)	213	85 [63; 87] 121 (56.8)	0.64 [0.49; 0.84]	< 0.001
Total					Interaction:	0.0498
Physical functioning						
Age						
≤ 65 years	241	169 [141; 256] 119 (49.4)	233	168 [113; 285] 97 (41.6)	1.00 [0.77; 1.31]	0.984
> 65 years	223	155 [113; 289] 102 (45.7)	232	92 [81; 116] 117 (50.4)	0.67 [0.51; 0.88]	0.003
Total					Interaction:	0.041
Role functioning						
Age						
≤ 65 years	241	64 [57; 86] 150 (62.2)	233	113 [85; 141] 120 (51.5)	1.18 [0.93; 1.50]	0.166
> 65 years	223	86 [59; 114] 130 (58.3)	232	63 [54; 85] 134 (57.8)	0.76 [0.59; 0.96]	0.019
Total					Interaction:	0.008

(continued)

Table 16: Subgroups (time to event) – RCT, direct comparison: carfilzomib + dexamethasone vs. bortezomib + dexamethasone (continued)

Study Outcome Characteristic Subgroup	Carfilzomib + dexamethasone		Bortezomib + dexamethasone		Carfilzomib + dexamethasone vs. bortezomib + dexamethasone	
	N	Median time to event in days [95% CI] Patients with event n (%)	N	Median time to event in days [95% CI] Patients with event n (%)	HR [95% CI]	p-value
ENDEAVOR						
Health-related quality of life (data cut-off 10 November 2014)						
EORTC QLQ-C30 functional scales, time to deterioration by ≥ 10 points [in days]						
Cognitive functioning						
Number of prior therapies						
1	231	182 [116; 281] 114 (49.4)	229	113 [81; 139] 113 (49.3)	0.70 [0.54; 0.91]	0.006
2 or 3	233	139 [96; 169] 120 (51.5)	236	141 [88; 218] 102 (43.2)	1.00 [0.77; 1.31]	0.980
Total					Interaction:	0.023
Pretreatment with bortezomib						
Yes	250	142 [113; 225] 123 (49.2)	252	172 [120; 253] 100 (39.7)	1.07 [0.82; 1.40]	0.586
No	214	141 [113; 224] 111 (51.9)	213	81 [57; 113] 115 (54.0)	0.64 [0.49; 0.83]	< 0.001
Total					Interaction:	0.002

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NA: not achieved; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20; RCT: randomized controlled trial; vs.: versus

Relevant effect modifications for different outcomes on morbidity and health-related quality of life were available. The subgroup characteristic "prior bortezomib therapy" was shown consistently across several outcomes to be a relevant subgroup characteristic. The subgroup results are described below.

Morbidity

Symptoms

There was an effect modification by the characteristic "number of prior therapies" and an effect modification by the characteristic "prior bortezomib therapy" for the outcome **"nausea and vomiting"**. Since the characteristic "prior bortezomib therapy" already is a relevant effect

modifier for several other outcomes, only this characteristic is considered below: There was no statistically significant difference between the treatment arms for patients with prior bortezomib therapy. This resulted in no hint of an added benefit of carfilzomib + dexamethasone in comparison with bortezomib + dexamethasone for these patients; an added benefit is therefore not proven. A statistically significant difference in favour of carfilzomib + dexamethasone was shown for patients without prior bortezomib therapies. This resulted in a hint of an added benefit of carfilzomib + dexamethasone in comparison with bortezomib + dexamethasone.

There was an effect modification by the characteristic "prior bortezomib therapy" for the outcome **"side effects of treatment"**. There was no statistically significant difference between the treatment arms for patients with prior bortezomib therapy. This resulted in no hint of an added benefit of carfilzomib + dexamethasone in comparison with bortezomib + dexamethasone for these patients; an added benefit is therefore not proven. A statistically significant difference in favour of carfilzomib + dexamethasone was shown for patients without prior bortezomib therapies. This resulted in a hint of an added benefit of carfilzomib + dexamethasone in comparison with bortezomib + dexamethasone. For the interpretation of this outcome, see also Section 2.2.1.3.

Health-related quality of life

There was an effect modification by the characteristic "prior bortezomib therapy" for the outcome **"global health status"**. There was no statistically significant difference between the treatment arms for patients with prior bortezomib therapy. This resulted in no hint of an added benefit of carfilzomib + dexamethasone in comparison with bortezomib + dexamethasone for these patients; an added benefit is therefore not proven. A statistically significant difference in favour of carfilzomib + dexamethasone was shown for patients without prior bortezomib therapies. This resulted in a hint of an added benefit of carfilzomib + dexamethasone in comparison with bortezomib + dexamethasone.

There was an effect modification by the characteristic "age" for the outcome **"physical functioning"**. There was no statistically significant difference between the treatment arms for patients ≤ 65 years. This resulted in no hint of an added benefit of carfilzomib + dexamethasone in comparison with bortezomib + dexamethasone for these patients; an added benefit is therefore not proven. A statistically significant difference in favour of carfilzomib + dexamethasone was shown for patients > 65 years. This resulted in a hint of an added benefit of carfilzomib + dexamethasone in comparison with bortezomib + dexamethasone.

There was an effect modification by the characteristic "age" for the outcome **"role functioning"**. There was no statistically significant difference between the treatment arms for patients ≤ 65 years. This resulted in no hint of an added benefit of carfilzomib + dexamethasone in comparison with bortezomib + dexamethasone for these patients; an added benefit is therefore not proven. A statistically significant difference in favour of carfilzomib + dexamethasone was shown for patients > 65 years. This resulted in a hint of an added benefit of carfilzomib + dexamethasone in comparison with bortezomib + dexamethasone.

There was an effect modification by the characteristic "number of prior therapies" and an effect modification by the characteristic "prior bortezomib therapy" for the outcome **"cognitive functioning"**. Since the characteristic "prior bortezomib therapy" already is a relevant effect modifier for several other outcomes, only this characteristic is considered below: There was no statistically significant difference between the treatment arms for patients with prior bortezomib therapy. This resulted in no hint of an added benefit of carfilzomib + dexamethasone in comparison with bortezomib + dexamethasone for these patients; an added benefit is therefore not proven. A statistically significant difference in favour of carfilzomib + dexamethasone was shown for patients without prior bortezomib therapies. This resulted in a hint of an added benefit of carfilzomib + dexamethasone in comparison with bortezomib + dexamethasone.

2.2.2 Probability and extent of added benefit

The derivation of probability and extent of the added benefit under consideration of the data subsequently submitted by the company in the commenting procedure is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [6].

2.2.2.1 Assessment of the added benefit at outcome level

Based on the results presented in Section 2.2.1, the extent of the respective added benefit at outcome level is estimated in the following Table 17.

Table 17: Extent of added benefit at outcome level: carfilzomib + dexamethasone vs. bortezomib + dexamethasone

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Carfilzomib + dexamethasone vs. bortezomib + dexamethasone** **Median time to event or proportion of events or LSME** **Effect estimate [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
Overall survival	47.6 vs. 40.0 months HR: 0.79 [0.65; 0.96]; p = 0.020 probability: "indication"	Outcome category: "mortality" $0.95 \leq CI_u < 1.00$ Added benefit, extent: "minor"
Morbidity		
EORTC QLQ-C30 (symptom scales) – time to deterioration		
Fatigue	57 vs. 57 days HR: 0.90 [0.76; 1.06]; p = 0.199	Lesser benefit/added benefit not proven
Nausea/vomiting		
Prior bortezomib therapy		
Yes	399 vs. 284 days HR: 0.96 [0.70; 1.31]; p = 0.781	Lesser benefit/added benefit not proven
No	NA vs. 197 days HR: 0.61 [0.44; 0.85]; p = 0.003 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ Added benefit, extent: "minor"
Pain	169 vs. 121 days HR: 0.86 [0.72; 1.04]; p = 0.128	Lesser benefit/added benefit not proven
Dyspnoea	86 vs. 113 days HR: 1.11 [0.93; 1.33]; p = 0.242	Lesser benefit/added benefit not proven
Insomnia	111 vs. 85 days HR: 0.80 [0.67; 0.95]; p = 0.013	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Lesser benefit/added benefit not proven[c]
Appetite loss	337 vs. 166 days HR: 0.66 [0.54; 0.81]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ Added benefit, extent: "minor"
Diarrhoea	309 vs. 169 days HR: 0.71 [0.58; 0.88]; p = 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ Added benefit, extent: "minor"

(continued)

Table 17: Extent of added benefit at outcome level: carfilzomib + dexamethasone vs. bortezomib + dexamethasone (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Carfilzomib + dexamethasone vs. bortezomib + dexamethasone** **Median time to event or proportion of events or LSME** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Morbidity		
EORTC QLQ-C30 (symptom scales) – time to deterioration		
Constipation	NA vs. 141 days HR: 0.47 [0.38; 0.59]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: "considerable"
EORTC QLQ-MY20 – time to deterioration		
Disease-related symptoms	393 vs. 250 days HR: 0.88 [0.71; 1.10]; p = 0.271	Lesser benefit/added benefit not proven
Side effects of treatment		
Prior bortezomib therapy		
Yes	195 vs. 120 days HR: 0.82 [0.63; 1.06]; p = 0.127	Lesser benefit/added benefit not proven
No	196 vs. 86 days HR: 0.52 [0.40; 0.68]; p < 0.001 probability: "hint"	Outcome category "non-serious/non-severe symptoms/late complications" $CI_u < 0.80$ Added benefit, extent: "considerable"
FACT/GOG-Ntx		
Neurotoxicity	LSME: 36.0 vs. 35.2 LSMD: 0.84 [0.40; 1.28]; p < 0.001 Hedges' g: 0.25 [0.12; 0.38][d]	Lesser benefit/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 (functional scales) – time to deterioration		
Global health status		
Prior bortezomib therapy		
Yes	88 vs. 106 days HR: 0.92 [0.72; 1.17]; p = 0.465	Lesser benefit/added benefit not proven
No	141 vs. 85 days HR: 0.64 [0.49; 0.84]; p < 0.001 probability: "hint"	Outcome category: "health-related quality of life" $0.75 \leq CI_u < 0.90$ Added benefit, extent: "considerable"

(continued)

Table 17: Extent of added benefit at outcome level: carfilzomib + dexamethasone vs. bortezomib + dexamethasone (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Carfilzomib + dexamethasone vs. bortezomib + dexamethasone** **Median time to event or proportion of events or LSME** **Effect estimate [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Health-related quality of life		
EORTC QLQ-C30 (functional scales) – time to deterioration		
Physical functioning		
Age		
≤ 65 years	169 vs. 168 days HR: 1.00 [0.77; 1.31]; p = 0.984	Lesser benefit/added benefit not proven
> 65 years	155 vs. 92 days HR: 0.67 [0.51; 0.88]; p = 0.003 probability: "hint"	Outcome category: "health-related quality of life" $0.75 \leq CI_u < 0.90$ Added benefit, extent: "considerable"
Role functioning		
Age		
≤ 65 years	64 vs. 113 days HR: 1.18 [0.93; 1.50]; p = 0.166	Lesser benefit/added benefit not proven
> 65 years	86 vs. 63 days HR: 0.76 [0.59; 0.96]; p = 0.019 probability: "hint"	Outcome category: "health-related quality of life" $0.90 \leq CI_u < 1.00$ Added benefit, extent: "minor"
Emotional functioning	211 vs. 193 days HR: 0.86 [0.70; 1.05]; p = 0.138	Lesser benefit/added benefit not proven
Cognitive functioning		
Prior bortezomib therapy		
Yes	142 vs. 172 days HR: 1.07 [0.82; 1.40]; p = 0.586	Lesser benefit/added benefit not proven
No	141 vs. 81 days HR: 0.64 [0.49; 0.83]; p < 0.001 probability: "hint"	Outcome category: "health-related quality of life" $0.75 \leq CI_u < 0.90$ Added benefit, extent: "considerable"
Social functioning	85 vs. 85 days HR: 0.84 [0.70; 1.00]; p = 0.046 probability: "hint"	Outcome category: "health-related quality of life" $0.90 \leq CI_u < 1.00$ Added benefit, extent: "minor"
EORTC QLQ-MY20 – time to deterioration		
Future perspective	56 vs. 50 days HR: 1.01 [0.86; 1.19]; p = 0.916	Lesser benefit/added benefit not proven
Body image	NA vs. NA HR: 1.20 [0.92; 1.58]; p = 0.176	Lesser benefit/added benefit not proven

(continued)

Table 17: Extent of added benefit at outcome level: carfilzomib + dexamethasone vs. bortezomib + dexamethasone (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Carfilzomib + dexamethasone vs. bortezomib + dexamethasone** **Median time to event or proportion of events or LSME** **Effect estimate [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Side effects		
SAEs	10.9 vs. 16.4 months HR: 1.22 [1.01; 1.47]; p = 0.040 HR: 0.82 [0.68; 0.99][e] probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Greater harm, extent: "minor"
Severe AEs (CTCAE grade ≥ 3)	3.1 vs. 2.9 months HR: 1.06 [0.92; 1.24]; p = 0.413	Greater/lesser harm not proven
Discontinuation due to AEs		
≥ 1 study medication	Proportion of events: 28.7 vs. 25.9% RR: 1.11 [0.90; 1.37]; p = 0.530	Greater/lesser harm not proven
Total study medication	Proportion of events: 25.1 vs. 21.7% RR: 1.15 [0.91; 1.46]; p = 0.248	

a: Probability provided if a statistically significant and relevant effect is present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
d: If the CI of Hedges' g is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, it cannot be derived that a relevant effect is present.
e: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; FACT/GOG-NTx: Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (subscale); HR: hazard ratio; LSMD: least squares mean difference; LSME: least squares mean estimate; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20; RR: relative risk; SAE: serious adverse event; vs.: versus

2.2.2.2 Overall conclusion on added benefit

Table 18 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 18: Positive and negative effects from the assessment of carfilzomib + dexamethasone vs. bortezomib + dexamethasone

Positive effects	**Negative effects**
Mortality ▪ overall survival: indication of an added benefit – extent: “minor”	–
Health-related quality of life ▪ social functioning: hint of an added benefit – extent: “minor” ▪ global health status and cognitive functioning: ▫ without prior bortezomib therapy: hint of an added benefit – extent: “considerable” ▪ physical functioning ▫ > 65 years: hint of an added benefit – extent: “considerable” ▪ role functioning ▫ > 65 years: hint of an added benefit – extent: “minor”	–
–	Serious/severe side effects: ▪ SAEs: hint of greater harm – extent: “minor”
Non-serious/non-severe symptoms/late complications ▪ appetite loss and diarrhoea: hint of an added benefit – extent: “minor” ▪ constipation: hint of an added benefit – extent “considerable” ▪ side effects of treatment ▫ without prior bortezomib therapy: hint of an added benefit – extent: “considerable” ▪ nausea and vomiting ▫ without prior bortezomib therapy: hint of an added benefit – extent: “minor”	–
There were no usable data for specific AEs.	
AE: adverse event; SAE: serious adverse event; vs.: versus	

Overall, there are positive and negative effects.

On the positive side, there is an indication of a minor added benefit for the outcome “overall survival”. In addition, there are hints of an added benefit of different extent, some of which only for individual subgroups, in the outcome categories of health-related quality of life and morbidity.

These positive effects are accompanied by a hint of greater harm in SAEs on the side of negative effects.

No conclusions could be drawn for specific AEs because no usable data were available.

In the overall consideration, there is an indication of a minor added benefit of carfilzomib + dexamethasone in comparison with bortezomib + dexamethasone for patients with multiple myeloma who have received at least one prior therapy.

2.2.3 List of included studies

ENDEAVOR

Amgen. Phase 3 Study With Carfilzomib and Dexamethasone Versus Bortezomib and Dexamethasone for Relapsed Multiple Myeloma Patients: full text view [online]. In: ClinicalTrials.gov, 25.08.2017. April 18, 2017 [Accessed: 28.08.2017]. URL: https://ClinicalTrials.gov/show/NCT01568866.

Amgen. Phase 3 Study With Carfilzomib and Dexamethasone Versus Bortezomib and Dexamethasone for Relapsed Multiple Myeloma Patients: study results [online]. In: ClinicalTrials.gov, 25.08.2017. April 18, 2017 [Accessed: 28.08.2017]. URL: https://clinicaltrials.gov/ct2/show/results/NCT01568866.

Amgen. A Randomized, Open-label, Phase 3 Study of Carfilzomib Plus Dexamethasone vs. Bortezomib Plus Dexamethasone in Patients with Relapsed Multiple Myeloma; study ENDEAVOR; Clinical Study Protocol [unpublished]. 2015.

Amgen. A Randomized, Open-label, Phase 3 Study of Carfilzomib Plus Dexamethasone vs. Bortezomib Plus Dexamethasone in Patients with Relapsed Multiple Myeloma; study ENDEAVOR; Statstical Analysis Plan [unpublished]. 2015.

Amgen. A Randomized, Open-label, Phase 3 Study of Carfilzomib Plus Dexamethasone vs. Bortezomib Plus Dexamethasone in Patients with Relapsed Multiple Myeloma; study ENDEAVOR; Zusatzanalysen [unpublished]. 2017.

Amgen. A Randomized, Open-label, Phase 3 Study of Carfilzomib Plus Dexamethasone vs. Bortezomib Plus Dexamethasone in Patients with Relapsed Multiple Myeloma; study ENDEAVOR; Clinical Study Report [unpublished]. 2017.

Chng WJ, Goldschmidt H, Dimopoulos MA, Moreau P, Joshua D, Palumbo A et al. Carfilzomib-dexamethasone vs bortezomib-dexamethasone in relapsed or refractory multiple myeloma by cytogenetic risk in the phase 3 study ENDEAVOR. Leukemia 2016; 31(6): 1368-1374.

Dimopoulos MA, Moreau P, Palumbo A, Joshua D, Pour L, Hajek R et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. Lancet Oncol 2015; 17(1): 27-38.

Moreau P, Joshua D, Chng WJ, Palumbo A, Goldschmidt H, Hajek R et al. Impact of prior treatment on patients with relapsed multiple myeloma treated with carfilzomib and dexamethasone vs bortezomib and dexamethasone in the phase 3 ENDEAVOR study. Leukemia 2016; 31(1): 115-122.

Onyx Therapeutics Inc. A Randomized, Open-label, Phase 3 Study of Carfilzomib Plus Dexamethasone vs Bortezomib Plus Dexamethasone in Patients With Relapsed Multiple Myeloma [online]. In: EU Clinical Trials Register, 25.08.2017. [Accessed: 28.08.2017]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-000128-16.

2.3 Summary

The data subsequently submitted by the company in the commenting procedure changed the conclusion on the added benefit of carfilzomib from dossier assessment A17-38.

The following Table 19 shows the result of the benefit assessment of carfilzomib under consideration of dossier assessment A17-38 and the present addendum.

Table 19: Carfilzomib – probability and extent of added benefit

Therapeutic indication	**ACT[a, b]**	**Extent and probability of added benefit**
Adult patients with multiple myeloma who have received at least one prior therapy[c]	Bortezomib in combination with pegylated liposomal doxorubicin or **bortezomib in combination with dexamethasone** or **lenalidomide in combination with dexamethasone** or elotuzumab in combination with lenalidomide and dexamethasone	In combination with lenalidomide and dexamethasone: ▪ patients < 65 years: **indication of a considerable added benefit** ▪ patients ≥ 65 years: **hint of a minor added benefit** In combination with dexamethasone: ▪ **Indication of minor added benefit**
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b: It is assumed for the present therapeutic indication that the use of carfilzomib in combination with lenalidomide and dexamethasone or in combination with dexamethasone alone is conducted in the framework of a remission-inducing induction treatment. High-dose chemotherapy with stem cell transplantation, which may be a subsequent treatment option, is therefore not an option as part of the ACT. c: According to the approval, carfilzomib is used in combination with either lenalidomide and dexamethasone or dexamethasone alone. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The G-BA decides on the added benefit.

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Carfilzomib (multiples Myelom): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A17-38 [online]. 13.11.2017 [Accessed: 17.11.2017]. (IQWiG-Berichte; Volume 560). URL: https://www.iqwig.de/download/A17-38_Carfilzomib_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

2. Amgen. Carfilzomib (Kyprolis): Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 14.08.2017 [Accessed: 12.12.2017]. URL: https://www.g-ba.de/informationen/nutzenbewertung/308/#tab/dossier.

3. Amgen. Stellungnahme zum IQWiG-Bericht Nr. 560: Carfilzomib (multiples Myelom); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A17-38. [Soon available under: https://www.g-ba.de/informationen/nutzenbewertung/308/ in the document "Zusammenfassende Dokumentation"].

4. Gemeinsamer Bundesausschuss. Mündliche Anhörung gemäß 5. Kapitel § 19 Abs. 2 Verfahrensordnung des Gemeinsamen Bundesausschusses; hier: Wirkstoff Carfilzomib; stenographisches Wortprotokoll [online]. [Accessed: 23.01.2018]. URL: https://www.g-ba.de/informationen/nutzenbewertung/308/#tab/stellungnahmeverfahren.

5. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574.

6. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10.07.2017 [Accessed: 04.06.2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

7. Janssen. VELCADE 3,5 mg Pulver zur Herstellung einer Injektionslösung: Fachinformation [online]. 02.2017 [Accessed: 07.10.2017]. URL: http://www.fachinfo.de.

8. Amgen. Kyprolis 10 mg/30 mg/60 mg Pulver zur Herstellung einer Infusionslösung: Fachinformation [online]. 12.2016 [Accessed: 27.09.2017]. URL: https://www.fachinfo.de.

Appendix A – Kaplan-Meier curves (study ASPIRE)

The Kaplan-Meier curve on overall survival can be found in dossier assessment A17-38 [1].

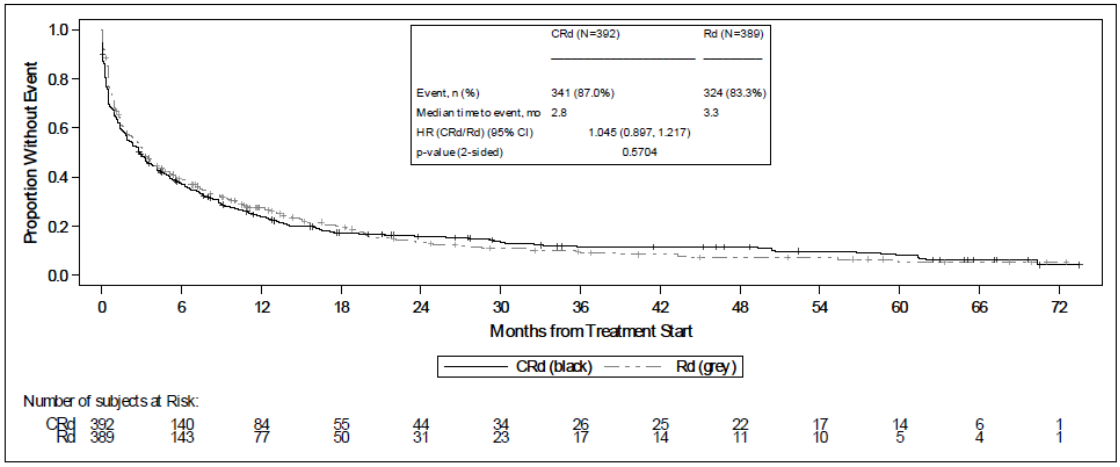

Figure 1: Kaplan-Meier curve for severe AEs (CTCAE grade ≥ 3) (second data cut-off 28 April 2017)

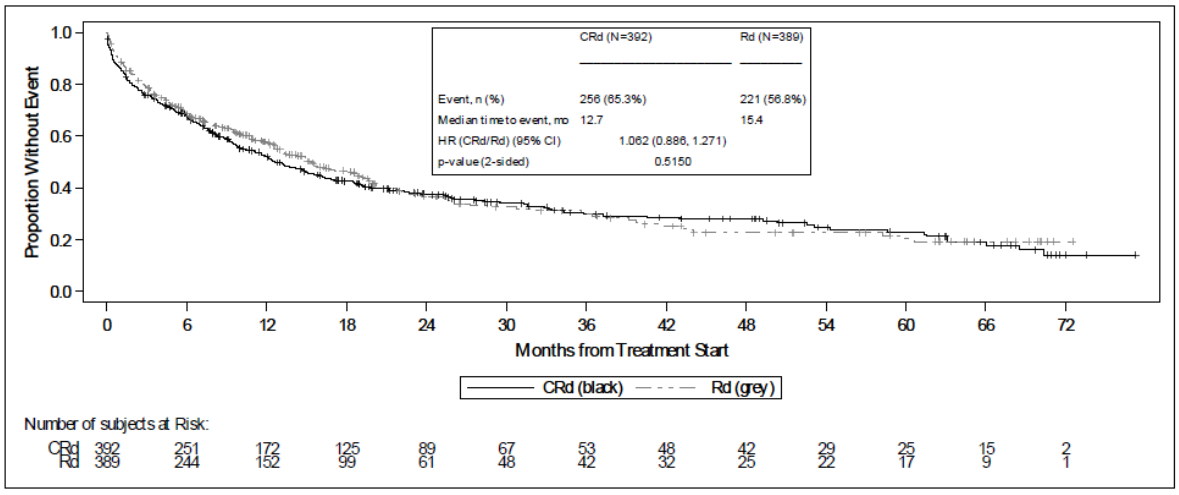

Figure 2: Kaplan-Meier curve for SAEs (second data cut-off 28 April 2017)

Appendix B – Results on side effects (study ASPIRE)

Table 20: Common AEs (in the SOC and in the PT ≥ 10% in at least one study arm) – RCT, direct comparison: carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone

Study	Patients with event n (%)	
SOC[a] PT[a]	**Carfilzomib + lenalidomide + dexamethasone N = 392**	**Lenalidomide + dexamethasone N = 389**
ASPIRE		
Overall rate of AEs (second data cut-off 28 April 2017)	384 (98.0)	381 (97.9)
Infections and infestations	314 (80.1)	279 (71.7)
Upper respiratory tract infection	118 (30.1)	81 (20.8)
Pneumonia	91 (23.2)	66 (17.0)
Viral upper respiratory tract infection	80 (20.4)	68 (17.5)
Bronchitis	79 (20.2)	59 (15.2)
Respiratory tract infection	46 (11.7)	42 (10.8)
General disorders and administration site conditions	269 (68.6)	245 (63.0)
Fatigue	131 (33.4)	124 (31.9)
Pyrexia	117 (29.8)	84 (21.6)
Oedema peripheral	77 (19.6)	65 (16.7)
Asthenia	73 (18.6)	57 (14.7)
Gastrointestinal disorders	267 (68.1)	228 (58.6)
Diarrhoea	174 (44.4)	145 (37.3)
Nausea	82 (20.9)	56 (14.4)
Constipation	81 (20.7)	70 (18.0)
Vomiting	49 (12.5)	33 (8.5)
Blood and lymphatic system disorders	253 (64.5)	241 (62.0)
Anaemia	169 (43.1)	158 (40.6)
Neutropenia	157 (40.1)	136 (35.0)
Thrombocytopenia	115 (29.3)	93 (23.9)
Metabolism and nutrition disorders	235 (59.9)	180 (46.3)
Hypokalaemia	116 (29.6)	58 (14.9)
Hypocalcaemia	66 (16.8)	48 (12.3)
Hypophosphataemia	57 (14.5)	33 (8.5)
Hyperglycaemia	50 (12.8)	39 (10.0)
Decreased appetite	47 (12.0)	35 (9.0)
Hypomagnesaemia	40 (10.2)	29 (7.5)

(continued)

Table 20: Common AEs (in the SOC and in the PT ≥ 10% in at least one study arm) – RCT, direct comparison: carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone (continued)

Study	**Patients with event n (%)**	
SOC[a] PT[a]	**Carfilzomib + lenalidomide + dexamethasone N = 392**	**Lenalidomide + dexamethasone N = 389**
ASPIRE		
Musculoskeletal and connective tissue disorders	232 (59.2)	217 (55.8)
Muscle spasms	106 (27.0)	82 (21.1)
Back pain	72 (18.4)	83 (21.3)
Arthralgia	57 (14.5)	58 (14.9)
Pain in extremity	48 (12.2)	43 (11.1)
Respiratory, thoracic and mediastinal disorders	223 (56.9)	165 (42.4)
Cough	116 (29.6)	70 (18.0)
Dyspnoea	78 (19.9)	59 (15.2)
Nervous system disorders	198 (50.5)	196 (50.4)
Headache	56 (14.3)	32 (8.2)
Dizziness	53 (13.5)	44 (11.3)
Skin and subcutaneous tissue disorders	152 (38.8)	133 (34.2)
Rash	52 (13.3)	60 (15.4)
Vascular disorders	152 (38.8)	100 (25.7)
Hypertension	62 (15.8)	31 (8.0)
Psychiatric disorders	140 (35.7)	120 (30.8)
Insomnia	81 (20.7)	65 (16.7)
Eye disorders	105 (26.8)	76 (19.5)
Cataract	44 (11.2)	37 (9.5)

a: MedDRA version 20.0.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 21: Common SAEs (in the SOC and in the PT ≥ 2% in at least one study arm) – RCT, direct comparison: carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone

Study	**Patients with event n (%)**	
SOC[a] PT[a]	**Carfilzomib + lenalidomide + dexamethasone N = 392**	**Lenalidomide + dexamethasone N = 389**
ASPIRE		
Overall rate of SAEs (second data cut-off 28 April 2017)	257 (65.6)	221 (56.8)
Infections and infestations	133 (33.9)	107 (27.5)
Pneumonia	67 (17.1)	52 (13.4)
Respiratory tract infection	16 (4.1)	8 (2.1)
Bronchitis	9 (2.3)	11 (2.8)
Cardiac disorders	47 (12.0)	30 (7.7)
Atrial fibrillation	9 (2.3)	8 (2.1)
Respiratory, thoracic and mediastinal disorders	39 (9.9)	24 (6.2)
Pulmonary embolism	12 (3.1)	8 (2.1)
General disorders and administration site conditions	35 (8.9)	28 (7.2)
Pyrexia	14 (3.6)	11 (2.8)
Progression of a disease	4 (1.0)	8 (2.1)
Gastrointestinal disorders	25 (6.4)	20 (5.1)
Diarrhoea	7 (1.8)	9 (2.3)
Blood and lymphatic system disorders	21 (5.4)	23 (5.9)
Anaemia	8 (2.0)	10 (2.6)
Febrile neutropenia	8 (2.0)	4 (1.0)
Nervous system disorders	21 (5.4)	27 (6.9)
Cerebrovascular accident	4 (1.0)	10 (2.6)
Vascular disorders	18 (4.6)	15 (3.9)
Deep vein thrombosis	9 (2.3)	6 (1.5)
Renal and urinary disorders	13 (3.3)	9 (2.3)
Acute kidney injury	8 (2.0)	4 (1.0)

a: MedDRA version 20.0.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Table 22: Common CTCAE grade ≥ 3 AEs (in the SOC and in the PT ≥ 3% in at least one study arm) – RCT, direct comparison: carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone

Study	**Patients with event n (%)**	
SOC[a] PT[a]	**Carfilzomib + lenalidomide + dexamethasone N = 392**	**Lenalidomide + dexamethasone N = 389**
ASPIRE		
Overall rate of CTCAE grade ≥ 3 AEs (second data cut-off 28 April 2017)	341 (87.0)	323 (83.0)
Blood and lymphatic system disorders	172 (43.9)	171 (44.0)
Neutropenia	122 (31.1)	107 (27.5)
Anaemia	73 (18.6)	68 (17.5)
Thrombocytopenia	66 (16.8)	51 (13.1)
Leukopenia	12 (3.1)	16 (4.1)
Cardiac disorders	48 (12.2)	28 (7.2)
Eye disorders	21 (5.4)	22 (5.7)
Cataract	20 (5.1)	17 (4.4)
Gastrointestinal disorders	49 (12.5)	43 (11.1)
Diarrhoea	18 (4.6)	17 (4.4)
General disorders and administration site conditions	75 (19.1)	54 (13.9)
Fatigue	32 (8.2)	26 (6.7)
Asthenia	14 (3.6)	8 (2.1)
Hepatobiliary disorders	14 (3.6)	8 (2.1)
Infections and infestations	129 (32.9)	106 (27.2)
Pneumonia	63 (16.1)	47 (12.1)
Respiratory tract infection	17 (4.3)	10 (2.6)
Bronchitis	8 (2.0)	12 (3.1)
Injury, poisoning and procedural complications	14 (3.6)	14 (3.6)
Investigations	59 (15.1)	42 (10.8)
Neutrophil count decreased	13 (3.3)	11 (2.8)
Platelet count decreased	13 (3.3)	9 (2.3)
Metabolism and nutrition disorders	115 (29.3)	76 (19.5)
Hypokalaemia	41 (10.5)	23 (5.9)
Hypophosphataemia	35 (8.9)	20 (5.1)
Hyperglycaemia	21 (5.4)	18 (4.6)
Hypocalcaemia	13 (3.3)	7 (1.8)

(continued)

Table 22: Common CTCAE grade ≥ 3 AEs (in the SOC and in the PT ≥ 3% in at least one study arm) – RCT, direct comparison: carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone (continued)

Study	**Patients with event n (%)**	
SOC[a] PT[a]	**Carfilzomib + lenalidomide + dexamethasone N = 392**	**Lenalidomide + dexamethasone N = 389**
ASPIRE		
Musculoskeletal and connective tissue disorders	41 (10.5)	58 (14.9)
Back pain	6 (1.5)	12 (3.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	15 (3.8)	20 (5.1)
Nervous system disorders	43 (11.0)	53 (13.6)
Psychiatric disorders	28 (7.1)	22 (5.7)
Insomnia	12 (3.1)	11 (2.8)
Renal and urinary disorders	21 (5.4)	15 (3.9)
Respiratory, thoracic and mediastinal disorders	47 (12.0)	32 (8.2)
Pulmonary embolism	12 (3.1)	9 (2.3)
Skin and subcutaneous tissue disorders	11 (2.8)	13 (3.3)
Vascular disorders	47 (12.0)	26 (6.7)
Hypertension	21 (5.4)	9 (2.3)

a: MedDRA version 20.0.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 23: Common discontinuations due to AEs (in the SOC or in the PT ≥ 1% in at least one study arm) – RCT, direct comparison: carfilzomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone

Study	**Patients with event n (%)**	
SOC[a] PT[a]	**Carfilzomib + lenalidomide + dexamethasone N = 392**	**Lenalidomide + dexamethasone N = 389**
ASPIRE		
Overall rate of discontinuations due to AEs[b] (second data cut-off 28 April 2017)	75 (19.1)	80 (20.6)
Blood and lymphatic system disorders	1 (0.3)	6 (1.5)
Cardiac disorders	12 (3.1)	9 (2.3)
Gastrointestinal disorders	3 (0.8)	4 (1.0)
General disorders and administration site conditions	8 (2.0)	7 (1.8)
Infections and infestations	19 (4.8)	11 (2.8)
Pneumonia	7 (1.8)	5 (1.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10 (2.6)	13 (3.3)
Myelodysplastic syndrome	1 (0.3)	4 (1.0)
Nervous system disorders	6 (1.5)	11 (2.8)
Cerebrovascular accident	1 (0.3)	4 (1.0)
Psychiatric disorders	5 (1.3)	1 (0.3)
Renal and urinary disorders	2 (0.5)	4 (1.0)
Respiratory, thoracic and mediastinal disorders	5 (1.3)	4 (1.0)

a: MedDRA version 20.0.
b: Discontinuation of entire study medication.
AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Appendix C – Kaplan-Meier curves (study ENDEAVOR)

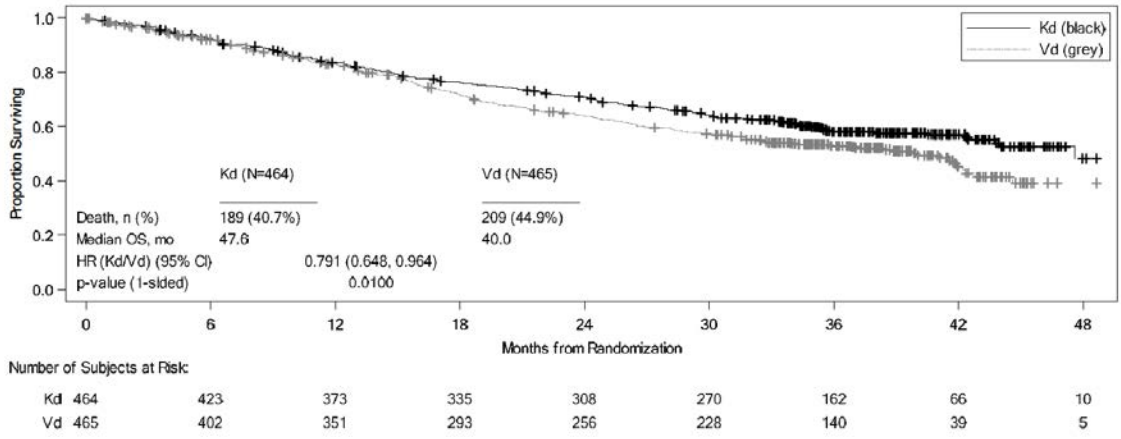

Figure 3: Kaplan-Meier curve for overall survival (second data cut-off 3 January 2017)

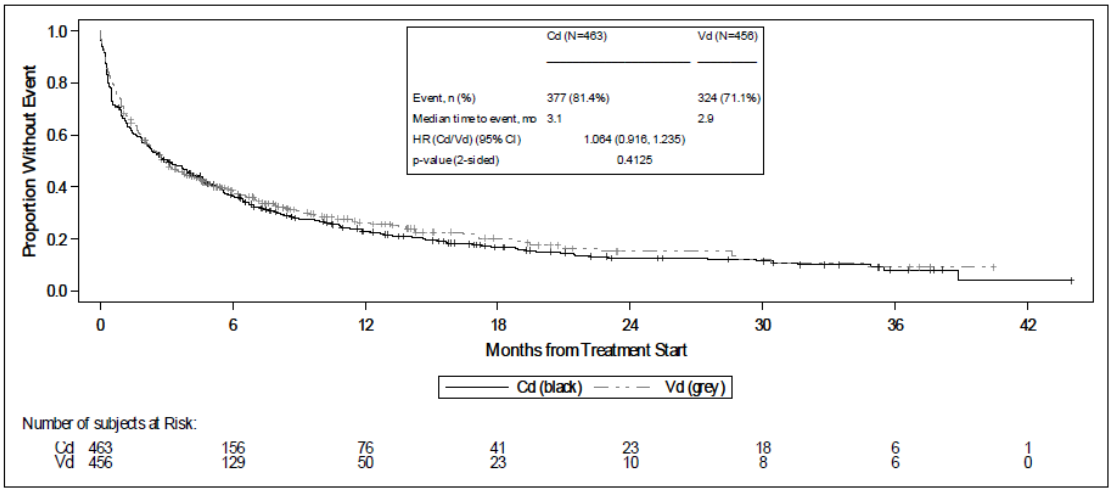

Figure 4: Kaplan-Meier curve for severe AEs (CTCAE grade ≥ 3) (second data cut-off 3 January 2017)

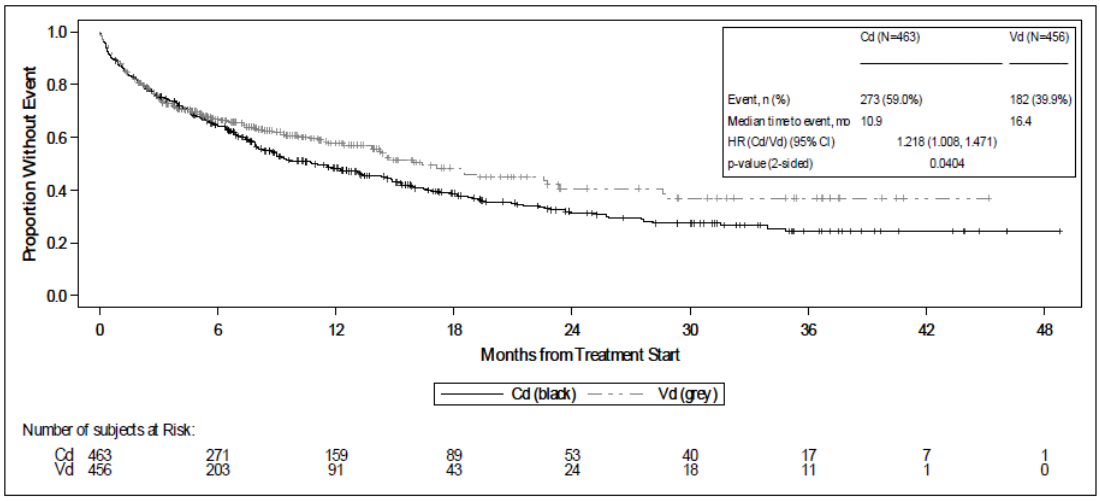

Figure 5: Kaplan-Meier curve for SAEs (second data cut-off 3 January 2017)

Appendix D – Results on side effects (study ENDEAVOR)

Table 24: Common AEs (in the SOC and in the PT ≥ 10% in at least one study arm) – RCT, direct comparison: carfilzomib + dexamethasone vs. bortezomib + dexamethasone

Study	Patients with event n (%)	
SOC[a] PT[a]	Carfilzomib + dexamethasone N = 463	Bortezomib + dexamethasone N = 456
ENDEAVOR		
Overall rate of AEs	457 (98.7)	451 (98.9)
Infections and infestations	366 (79.0)	312 (68.4)
Upper respiratory tract infection	119 (25.7)	83 (18.2)
Bronchitis	108 (23.3)	48 (10.5)
Nasopharyngitis	81 (17.5)	61 (13.4)
Pneumonia	53 (11.4)	53 (11.6)
Respiratory tract infection	51 (11.0)	32 (7.0)
General disorders and administration site conditions	360 (77.8)	305 (66.9)
Pyrexia	150 (32.4)	70 (15.4)
Fatigue	149 (32.2)	140 (30.7)
Oedema peripheral	116 (25.1)	87 (19.1)
Asthenia	107 (23.1)	79 (17.3)
Gastrointestinal disorders	292 (63.1)	298 (65.4)
Diarrhoea	168 (36.3)	185 (40.6)
Nausea	109 (23.5)	91 (20.0)
Vomiting	77 (16.6)	45 (9.9)
Constipation	75 (16.2)	127 (27.9)
Respiratory, thoracic and mediastinal disorders	287 (62.0)	171 (37.5)
Dyspnoea	149 (32.2)	62 (13.6)
Cough	128 (27.6)	72 (15.8)
Musculoskeletal and connective tissue disorders	279 (60.3)	234 (51.3)
Back pain	107 (23.1)	81 (17.8)
Muscle spasms	92 (19.9)	28 (6.1)
Arthralgia	60 (13.0)	52 (11.4)
Bone pain	55 (11.9)	40 (8.8)
Pain in extremity	55 (11.9)	50 (11.0)
Muscular weakness	44 (9.5)	47 (10.3)
Blood and lymphatic system disorders	254 (54.9)	195 (42.8)
Anaemia	197 (42.5)	129 (28.3)
Thrombocytopenia	100 (21.6)	84 (18.4)

(continued)

Table 24: Common AEs (in the SOC and in the PT ≥ 10% in at least one study arm) – RCT, direct comparison: carfilzomib + dexamethasone vs. bortezomib + dexamethasone (continued)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Carfilzomib + dexamethasone** **N = 463**	**Bortezomib + dexamethasone** **N = 456**
ENDEAVOR		
Overall rate of AEs	457 (98.7)	451 (98.9)
Nervous system disorders	246 (53.1)	341 (74.8)
Headache	95 (20.5)	49 (10.7)
Neuropathy peripheral	49 (10.6)	130 (28.5)
Paraesthesia	43 (9.3)	76 (16.7)
Dizziness	42 (9.1)	70 (15.4)
Peripheral sensory neuropathy	29 (6.3)	70 (15.4)
Neuralgia	12 (2.6)	72 (15.8)
Vascular disorders	235 (50.8)	122 (26.8)
Hypertension	149 (32.2)	45 (9.9)
Metabolism and nutrition disorders	227 (49.0)	197 (43.2)
Hypokalaemia	60 (13.0)	51 (11.2)
Hyperglycaemia	54 (11.7)	42 (9.2)
Decreased appetite	50 (10.8)	62 (13.6)
Investigations	216 (46.7)	154 (33.8)
Platelet count decreased	58 (12.5)	41 (9.0)
Blood creatinine increased	53 (11.4)	28 (6.1)
Psychiatric disorders	183 (39.5)	182 (39.9)
Insomnia	125 (27.0)	122 (26.8)
Skin and subcutaneous tissue disorders	150 (32.4)	139 (30.5)
Eye disorders	122 (26.3)	124 (27.2)
Cardiac disorders	118 (25.5)	51 (11.2)
Renal and urinary disorders	111 (24.0)	71 (15.6)
Injury, poisoning and procedural complications	99 (21.4)	96 (21.1)
Ear and labyrinth disorders	49 (10.6)	40 (8.8)

a: MedDRA version 15.1.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 25: Common SAEs (in the SOC and in the PT ≥ 2% in at least one study arm) – RCT, direct comparison: carfilzomib + dexamethasone vs. bortezomib + dexamethasone

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Carfilzomib + dexamethasone N = 463**	**Bortezomib + dexamethasone N = 456**
ENDEAVOR		
Overall rate of SAEs	273 (59.0)	182 (39.9)
Infections and infestations	132 (28.5)	83 (18.2)
Pneumonia	39 (8.4)	42 (9.2)
Respiratory tract infection	10 (2.2)	5 (1.1)
Respiratory, thoracic and mediastinal disorders	51 (11.0)	15 (3.3)
Dyspnoea	18 (3.9)	1 (0.2)
Pulmonary embolism	10 (2.2)	3 (0.7)
General disorders and administration site conditions	42 (9.1)	20 (4.4)
Pyrexia	19 (4.1)	3 (0.7)
Cardiac disorders	39 (8.4)	18 (3.9)
Nervous system disorders	23 (5.0)	19 (4.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	21 (4.5)	5 (1.1)
Renal and urinary disorders	21 (4.5)	11 (2.4)
Renal failure acute	11 (2.4)	7 (1.5)
Gastrointestinal disorders	20 (4.3)	30 (6.6)
Diarrhoea	5 (1.1)	11 (2.4)
Musculoskeletal and connective tissue disorders	19 (4.1)	10 (2.2)
Vascular disorders	17 (3.7)	12 (2.6)
Blood and lymphatic system disorders	15 (3.2)	9 (2.0)
Injury, poisoning and procedural complications	13 (2.8)	10 (2.2)
Metabolism and nutrition disorders	12 (2.6)	14 (3.1)

a: MedDRA version 15.1.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Table 26: Common CTCAE grade ≥ 3 AEs (in the SOC and in the PT ≥ 3% in at least one study arm) – RCT, direct comparison: carfilzomib + dexamethasone vs. bortezomib + dexamethasone

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Carfilzomib + dexamethasone N = 463**	**Bortezomib + dexamethasone N = 456**
ENDEAVOR		
Overall rate of AEs with CTCAE grade ≥ 3	377 (81.4)	324 (71.1)
Infections and infestations	145 (31.3)	94 (20.6)
Pneumonia	42 (9.1)	39 (8.6)
Blood and lymphatic system disorders	127 (27.4)	92 (20.2)
Anaemia	76 (16.4)	46 (10.1)
Thrombocytopenia	41 (8.9)	43 (9.4)
Lymphopenia	22 (4.8)	14 (3.1)
General disorders and administration site conditions	96 (20.7)	72 (15.8)
Fatigue	31 (6.7)	35 (7.7)
Asthenia	21 (4.5)	14 (3.1)
Pyrexia	14 (3.0)	3 (0.7)
Metabolism and nutrition disorders	86 (18.6)	62 (13.6)
Hyperglycaemia	22 (4.8)	17 (3.7)
Hypophosphataemia	15 (3.2)	6 (1.3)
Hypokalaemia	11 (2.4)	17 (3.7)
Vascular disorders	85 (18.4)	32 (7.0)
Hypertension	67 (14.5)	15 (3.3)
Investigations	84 (18.1)	52 (11.4)
Lymphocyte count decreased	29 (6.3)	9 (2.0)
Platelet count decreased	18 (3.9)	24 (5.3)
Respiratory, thoracic and mediastinal disorders	59 (12.7)	29 (6.4)
Dyspnoea	29 (6.3)	10 (2.2)
Gastrointestinal disorders	49 (10.6)	68 (14.9)
Diarrhoea	18 (3.9)	39 (8.6)
Cardiac disorders	46 (9.9)	23 (5.0)
Musculoskeletal and connective tissue disorders	41 (8.9)	38 (8.3)
Back pain	10 (2.2)	14 (3.1)
Nervous system disorders	40 (8.6)	76 (16.7)
Neuropathy peripheral	6 (1.3)	28 (6.1)
Renal and urinary disorders	37 (8.0)	18 (3.9)

(continued)

Table 26: Common CTCAE grade ≥ 3 AEs (in the SOC and in the PT ≥ 3% in at least one study arm) – RCT, direct comparison: carfilzomib + dexamethasone vs. bortezomib + dexamethasone (continued)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Carfilzomib + dexamethasone N = 463**	**Bortezomib + dexamethasone N = 456**
ENDEAVOR		
Overall rate of AEs with CTCAE grade ≥ 3	377 (81.4)	324 (71.1)
Psychiatric disorders	27 (5.8)	23 (5.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	21 (4.5)	6 (1.3)
Eye disorders	15 (3.2)	13 (2.9)
SMQN[b]		
Neuropathy peripheral (CTCAE grade ≥ 3)	11 (2.4)	44 (9.6)

a: MedDRA version 15.1.
b: Used by the company for the assessment of the added benefit.
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SMQN: Standardized MedDRA Query (narrow scope) SOC: System Organ Class; vs.: versus

Table 27: Common discontinuations due to AEs (in the SOC and in the PT ≥ 1% in at least one study arm) – RCT, direct comparison: carfilzomib + dexamethasone vs. bortezomib + dexamethasone

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Carfilzomib + dexamethasone** **N = 463**	**Bortezomib + dexamethasone** **N = 456**
ENDEAVOR		
Overall rate of discontinuations due to AEs	116 (25.1)	99 (21.7)
Cardiac disorders	25 (5.4)	4 (0.9)
Cardiac failure	8 (1.7)	0 (0)
General disorders and administration site conditions	18 (3.9)	15 (3.3)
Asthenia	5 (1.1)	2 (0.4)
Fatigue	2 (0.4)	6 (1.3)
Respiratory, thoracic and mediastinal disorders	16 (3.5)	7 (1.5)
Dyspnoea	4 (0.9)	6 (1.3)
Infections and infestations	14 (3.0)	8 (1.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10 (2.2)	1 (0.2)
Nervous system disorders	10 (2.2)	46 (10.1)
Investigations	6 (1.3)	7 (1.5)
Ejection fraction decreased	5 (1.1)	3 (0.7)
Metabolism and nutrition disorders	6 (1.3)	6 (1.3)
Renal and urinary disorders	6 (1.3)	2 (0.4)
Renal failure acute	5 (1.1)	2 (0.4)
Vascular disorders	6 (1.3)	1 (0.2)
Gastrointestinal disorders	4 (0.9)	15 (3.3)
Diarrhoea	1 (0.2)	6 (1.3)
Musculoskeletal and connective tissue disorders	4 (0.9)	5 (1.1)

a: MedDRA version 15.1.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus