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Carfilzomib (multiple myeloma) –

Addendum to Commission A21-08[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
C30	Core 30
EORTC QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D	European Quality of Life Questionnaire – 5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HR	hazard ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RR	relative risk
VAS	visual analogue scale

1 Background

On 25 May 2021, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A21-08 (Carfilzomib– Benefit assessment according to § 35a Social Code Book V) [1].

To assess the benefit of carfilzomib in combination with daratumumab and dexamethasone (hereinafter carfilzomib + daratumumab + dexamethasone) in comparison with the appropriate comparator therapy (ACT) in adult patients with multiple myeloma who received at least 1 prior therapy, the randomized controlled study CANDOR [2] was used. In the CANDOR study, carfilzomib + daratumumab + dexamethasone was compared with carfilzomib + dexamethasone. The benefit assessment used the results of the 2nd data cut-off, 15 June 2020.

The G-BA commissioned IQWiG with assessing the following data, which were subsequently submitted by the pharmaceutical company (hereinafter "company") together with its written comment [3], taking into account the data provided in the dossier [4].

- List of subsequent therapies at the 2nd data cut-off
- Results for the visual analogue scale (VAS) of the European Quality of Life Questionnaire – 5 Dimensions (EQ-5D): responder analyses with a response threshold of 15 points
- Results of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) Core 30 (C30): analyses of time to improvement
- Adverse events (AEs): results on the outcome of discontinuation due to AEs

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

2 Assessment

2.1 Results submitted later on subsequent therapies

For the CANDOR study, the dossier provided analyses of 2 data cut-offs. For the benefit assessment [1], only the planned 2nd data cut-off was used since it represents the longest available follow-up observation period. The company's dossier presented the patients' subsequent therapies only for the 1st data cut-off. With its written comment, the company later submitted the list of subsequent therapies received at the 2nd data cut-off. They are presented in Table 1.

Table 1: Information on subsequent antineoplastic therapies – RCT, direct comparison: carfilzomib + daratumumab + dexamethasone vs. carfilzomib + dexamethasone (multipage table)

Study / **Drug**	**Patients with subsequent therapy n (%)**	
	Carfilzomib + daratumumab + dexamethasone N = 312	**Carfilzomib + dexamethasone N = 154**
CANDOR (2nd data cut-off [15/06/2020])		
Total	107 (34.3)	84 (54.5)
Dexamethasone	65 (20.8)	50 (32.5)
Lenalidomide	46 (14.7)	34 (22.1)
Pomalidomide	31 (9.9)	22 (14.3)
Daratumumab	9 (2.9)	30 (19.5)
Cyclophosphamide	28 (9.0)	10 (6.5)
Bortezomib	13 (4.2)	15 (9.7)
Etoposide	9 (2.9)	5 (3.2)
Dexamethasone/lenalidomide	12 (3.8)	1 (0.6)
Ixazomib[a]	10 (3.2)	2 (1.3)
Bendamustine	7 (2.2)	5 (3.2)
Cisplatin	7 (2.2)	5 (3.2)
Doxorubicin	6 (1.9)	6 (3.9)
Melphalan	5 (1.6)	7 (4.5)
Investigational substance	7 (2.2)	2 (1.3)
Elotuzumab	6 (1.9)	3 (1.9)
Dexamethasone/pomalidomide	5 (1.6)	4 (2.6)
Thalidomide	6 (1.9)	2 (1.3)
Antineoplastic agents	3 (1.0)	5 (3.2)
Carfilzomib	4 (1.3)	3 (1.9)
Radiotherapy	5 (1.6)	1 (0.6)
Monoclonal antibodies	1 (0.3)	3 (1.9)
Cyclophosphamide/dexamethasone/lenalidomide	3 (1.0)	0 (0)
Fludarabine	3 (1.0)	0 (0)

Table 1: Information on subsequent antineoplastic therapies – RCT, direct comparison: carfilzomib + daratumumab + dexamethasone vs. carfilzomib + dexamethasone (multipage table)

Study **Drug**	**Patients with subsequent therapy n (%)**	
	Carfilzomib + daratumumab + dexamethasone **N = 312**	**Carfilzomib + dexamethasone** **N = 154**
Panobinostat	3 (1.0)	0 (0)
Venetoclax	3 (1.0)	0 (0)
Clarithromycin	2 (0.6)	1 (0.6)
Doxorubicin hydrochloride	2 (0.6)	1 (0.6)
Vincristine sulphate	2 (0.6)	1 (0.6)
Dexamethasone sodium phosphate	1 (0.3)	2 (1.3)
Prednisolone	1 (0.3)	2 (1.3)
Bortezomib/cyclophosphamide/dexamethasone	0 (0)	3 (1.9)
Clarithromycin/dexamethasone/lenalidomide	2 (0.6)	0 (0)
Immunostimulants	1 (0.3)	1 (0.6)

a. The company's comment also provides the following information on this drug: 1 (0.3) vs. 1 (0.6). This is implausible.

n: number of patients with follow-up therapy; N: number of analysed patients; RCT: randomized controlled trial

In both study arms, the most frequently received subsequent therapies included the drugs dexamethasone, lenalidomide, and pomalidomide. In the comparator arm, patients often also received subsequent therapy with daratumumab. The subsequent therapies used at the 2nd data cut-off generally correspond to those received at the 1st data cut-off.

2.2 Subsequently submitted results on health status (EQ-5D VAS)

For the outcome of health status (measured using EQ-5D VAS), the company's dossier presented (a) analyses on time to deterioration using the response criteria of 7 and 10 points and (b) analyses of mean change from treatment start to study end. As discussed in the IQWiG General Methods [5,6], a response criterion should be predefined to cover at least 15% of the range of an instrument's scale (for post hoc analyses, exactly 15% of the range of the scale) in order to reflect with sufficient certainty a change that is perceivable for patients. This is not the case for the presented response criteria. Therefore, the dossier assessment relies on analyses of mean change from treatment start to study end.

With its comment, the company subsequently submitted analyses on time to deterioration of health status, as measured by EQ-5D VAS, using a response criterion of 15 points. This corresponds to 15% of the range of the EQ-5D VAS scale. These analyses are assessed below.

The risk of bias for the results on health status (EQ-5D VAS) is rated as high (see associated dossier assessment [1])

Table 2 shows the subsequently submitted analysis of health status (EQ-5D VAS).

Table 2: Results (health status) – RCT, direct comparison: carfilzomib + daratumumab + dexamethasone vs. carfilzomib + dexamethasone

Study **Outcome category** **Outcome**	**Carfilzomib + daratumumab + dexamethasone**		**Carfilzomib + dexamethasone**		**Carfilzomib + daratumumab + dexamethasone vs. carfilzomib + 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]; p-value[a]**
CANDOR (2nd data cut-off [15/06/2020])					
Health status					
EQ-5D VAS[b]	278	17.1 [11.0; 22.7] 138 (49.6)	132	8.4 [4.7; 17.1] 72 (54.5)	0.71 [0.53; 0.94]; 0.016

a: HR and 95% CI calculated using a nonstratified Cox model; p-value using a nonstratified log-rank test.
b. Time to deterioration, defined as a score decrease by at least 15 points from study start.

CI: confidence interval; EQ-5D: European Quality of Life – 5 Dimensions; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of included patients; RCT: randomized controlled trial; VAS: visual analogue scale

For the outcome of health status, measured by EQ-5D VAS, a statistically significant difference was found in favour of carfilzomib + daratumumab + dexamethasone versus carfilzomib + dexamethasone. The size of this effect, however, is no more than marginal for an outcome of the category of non-serious/non-severe symptoms/late complications. Consequently, there is no hint of added benefit of carfilzomib + daratumumab + dexamethasone in comparison with carfilzomib + dexamethasone; an added benefit is therefore not proven.

2.3 Subsequently submitted results on EORTC QLQ-C30

In its written comment, the company submitted additional analyses of EORTC QLQ-C30. These included, among others, analyses of the percentage of patients with an improvement by 10 or 15 points (as shown by the odds ratio) and responder analyses for time to improvement by 10 or 15 points for global health status. In an oncological indication, however, analyses of time to deterioration (which the company already presented in its dossier for EORTC QLQ-C30) are of primary relevance. Additionally, the results on time to improvement were submitted for only one scale of the EORTC QLQ-C30, but not for the other scales on symptoms – or on health-related quality of life. Therefore, the EORTC QLQ-C30 data submitted subsequently and selectively are inappropriate for the present benefit assessment.

The subsequently submitted time-to-event analyses of the EORTC QLQ-C30 for the response criterion of 10 points are presented, in line with the commission, in Appendix A. In light of the substantial differences in follow-up durations between treatment arms, the corresponding analyses of the percentages of patients with an improvement cannot be meaningfully interpreted.

2.4 Subsequently submitted results on the outcome of discontinuation due to AEs

For the outcome of discontinuation due to AEs, the company's dossier provided the result in the form of an odds ratio and relative risk (RR) as well as an absolute risk reduction. Due to substantial differences between treatment arms in terms of follow-up duration, however, hazard ratio (HR) results are relevant. The company subsequently submitted this result as part of its written comment. The result is presented in Table 3. Subgroup analyses for this outcome are not available.

Table 3: Results (AEs) – RCT, direct comparison: carfilzomib + daratumumab + dexamethasone vs. carfilzomib + dexamethasone

Study **Outcome category** **Outcome**	**Carfilzomib + daratumumab + dexamethasone**		**Carfilzomib + dexamethasone**		**Carfilzomib + daratumumab + dexamethasone vs. carfilzomib + 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[b]**
CANDOR (2nd data cut-off [15/06/2020])					
Side effects					
Discontinuation due to AEs (≥ 1 component)	308	NR 85 (27.6)	153	33.2 [ND] 38 (24.8)	0.93 [0.63; 1.36]; 0.702

a. HR and 95% CI from nonstratified Cox model
b. 2-sided p-value from nonstratified log rank test.

AE: adverse event; CI: confidence interval; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; ND: no data; NR: not reached; RCT: randomized controlled trial

For the outcome of discontinuation due to AEs, analysed by time-to-event analysis, no statistically significant difference between treatment groups was found. Consequently, there is no hint of added benefit of carfilzomib + daratumumab + dexamethasone versus carfilzomib + dexamethasone; an added benefit is therefore not proven.

2.5 Summary

The data subsequently submitted by the company in the commenting procedure do not change the conclusion on the added benefit of carfilzomib + daratumumab + dexamethasone drawn in

dossier assessment A21-08. Likewise, the additional evaluation of time-to-event analyses presented as supplementary information in the benefit assessment for time to deterioration in the EORTC QLQ-C30 by 10 points [1,7] does not change the conclusion on added benefit: a relevant favourable effect is found only for a single dimension of health-related quality of life (social functioning); in view of the currently available data, it is insufficient for establishing an added benefit.

Table 4 below shows the result of the benefit assessment of carfilzomib + daratumumab + dexamethasone in consideration of dossier assessment A21-08 and the present addendum.

Table 4: Carfilzomib + daratumumab + dexamethasone – probability and extent of added benefit

Indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with multiple myeloma who have received at least 1 prior therapy	▪ 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 or ▪ Carfilzomib in combination with lenalidomide and dexamethasone or ▪ **Carfilzomib in combination with dexamethasone** or ▪ Daratumumab in combination with lenalidomide and dexamethasone or ▪ Daratumumab in combination with bortezomib and dexamethasone	Added benefit not proven
a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is marked in **bold**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The G-BA decides on the added benefit.

3 References

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Appendix A – Supplementary presentation of the subsequently submitted EORTC QLQ-C30 results

Table 5: Results (supplementary presentation of EORTC QLQ-C30) – RCT, direct comparison: carfilzomib + daratumumab + dexamethasone vs. carfilzomib + dexamethasone

Study Outcome category Outcome	Carfilzomib + daratumumab + dexamethasone		Carfilzomib + dexamethasone		Carfilzomib + daratumumab + dexamethasone vs. carfilzomib + 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]; p-value[a]
CANDOR (2nd data cut-off [15/06/2020])					
EORTC QLQ-C30[b, c]	281	6.0 [4.6; 8.3] 170 (60.5)	128	6.7 [3.8; NC] 64 (50.0)	1.23 [0.92; 1.64]; 0.168

a. HR and 95 % CI calculated using a nonstratified Cox model; p-value using a nonstratified log rank test.
b. Time to improvement, defined as a score increase by at least 10 points from study start.
c. The analysis on time to improvement with the response criterion of 15 points results in the same numeric values.

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; QLQ-C30: Quality of Life Questionnaire-Core Module 30; RCT: randomized controlled trial