IQWiG Reports – Commission No. A21-08

Carfilzomib (multiple myeloma) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Carfilzomib (multiples Myelom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 April 2021). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AMQ	Amgen MedDRA Query
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EORTC QLQ-MY20	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Multiple Myeloma 20
EQ-5D	European Quality of Life-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)
ISS	International Staging System
MD	mean difference
MedDRA	Medical Dictionary for Regulatory Activities
PFS	progression-free survival
PT	Preferred Term
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug carfilzomib. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 15 January 2021.

Research question

The aim of the present report is the assessment of the added 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 have received at least one prior therapy.

The G-BA's specification of the ACT resulted in one research question, which is presented in the following Table 2.

Table 2: Research questions of the benefit assessment of carfilzomib + daratumumab + dexamethasone

Therapeutic indication	**ACT**[a]
Adult patients with multiple myeloma who have received at least one 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
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**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company chose carfilzomib in combination with dexamethasone (hereinafter "carfilzomib + dexamethasone") from the specified options as comparator therapy and thus followed the ACT defined by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used for the derivation of the added benefit.

Results

The CANDOR study was used for the benefit assessment.

Study design

The CANDOR study is an ongoing, open-label, randomized, active-controlled multicentre study on the comparison of carfilzomib + daratumumab + dexamethasone with carfilzomib + dexamethasone. The study included adult patients with relapsed or progressive multiple myeloma after last treatment who had received 1 to 3 prior lines of therapy. All patients had to have a general condition corresponding to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 2.

Patients included in the CANDOR study were randomly assigned in a 2:1 ratio to treatment with carfilzomib + daratumumab + dexamethasone (N = 312) or to treatment with carfilzomib + dexamethasone (N = 154).

Patients were treated until disease progression, unacceptable toxicity, withdrawal of consent or for a maximum of 4 years. Treatment in both study arms was largely in compliance with the requirements of the Summary of Product Characteristics (SPC).

Primary outcome of the CANDOR study was progression-free survival (PFS). Overall survival as well as outcomes on symptoms, health status, health-related quality of life and adverse events (AEs) were recorded as patient-relevant secondary and supplementary outcomes.

Results are available for 2 data cut-offs (first data cut-off: 14 July 2019; second data cut-off: 15 June 2020). The second data cut-off represents the longest available observation period and was used for the present benefit assessment.

Risk of bias

The risk of bias across outcomes was rated as low for the CANDOR study.

At outcome level, the risk of bias for the results of the outcome "overall survival" was rated as low; for the results of all other outcomes, the risk of bias was rated as high.

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

Results

Mortality

Overall survival

The CANDOR study showed no statistically significant difference between the treatment groups for the outcome "overall survival". This resulted in no hint of an added benefit of carfilzomib + daratumumab + dexamethasone in comparison with carfilzomib + dexamethasone; an added benefit is therefore not proven.

Morbidity

Symptoms (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire [EORTC QLQ]-Core 30 [C30])

There were no statistically significant differences between the treatment groups in any of the EORTC QLQ-C30 symptom scales (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea). In each case, this resulted in no hint of an added benefit of carfilzomib + daratumumab + dexamethasone in comparison with carfilzomib + dexamethasone; an added benefit is therefore not proven.

Symptoms (EORTC QLQ-Multiple Myeloma Module 20 [MY20])

There were no statistically significant differences between the treatment groups in any of the EORTC QLQ-MY20 symptom scales (disease-related symptoms, side effects). In each case, this resulted in no hint of an added benefit of carfilzomib + daratumumab + dexamethasone in comparison with carfilzomib + dexamethasone; an added benefit is therefore not proven.

Health status (European Quality of Life-5 Dimensions [EQ-5D] visual analogue scale [VAS])

There was no statistically significant difference between the treatment groups for the outcome "health status". This resulted in no hint of an added benefit of carfilzomib + daratumumab + dexamethasone in comparison with carfilzomib + dexamethasone; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

There were no statistically significant differences between the treatment groups in any of the EORTC QLQ-C30 scales on health-related quality of life (global health status, physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning). In each case, this resulted in no hint of an added benefit of carfilzomib + daratumumab + dexamethasone in comparison with carfilzomib + dexamethasone; an added benefit is therefore not proven.

EORTC QLQ-MY20

There were no statistically significant differences between the treatment groups in any of the EORTC QLQ-MY20 scales on health-related quality of life (body image, future perspective).

In each case, this resulted in no hint of an added benefit of carfilzomib + daratumumab + dexamethasone in comparison with carfilzomib + dexamethasone; an added benefit is therefore not proven.

Side effects

Serious AEs [SAEs], severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)

There was no statistically significant difference between the treatment groups for the outcomes "SAEs" and "severe AEs". In each case, this resulted in no hint of greater or lesser harm from carfilzomib + daratumumab + dexamethasone in comparison with carfilzomib + dexamethasone; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

There were no usable data for discontinuation due to AEs. This resulted in no hint of greater or lesser harm from carfilzomib + daratumumab + dexamethasone in comparison with carfilzomib + dexamethasone; greater or lesser harm is therefore not proven.

Infusion-related reactions

There were no usable data for infusion-related reactions. This resulted in no hint of greater or lesser harm from carfilzomib + daratumumab + dexamethasone in comparison with carfilzomib + dexamethasone; greater or lesser harm is therefore not proven.

Diarrhoea (AEs)

A statistically significant difference to the disadvantage of carfilzomib + daratumumab + dexamethasone was shown for the outcome "diarrhoea" (AEs). This resulted in a hint of greater harm from carfilzomib + daratumumab + dexamethasone in comparison with carfilzomib + dexamethasone.

Renal and urinary disorders (severe AEs)

A statistically significant difference in favour of carfilzomib + daratumumab + dexamethasone was shown for the outcome "renal and urinary disorders" (severe AEs). This resulted in a hint of lesser harm from carfilzomib + daratumumab + dexamethasone in comparison with carfilzomib + dexamethasone.

Thrombocytopenia (severe AEs)

A statistically significant difference to the disadvantage of carfilzomib + daratumumab + dexamethasone was shown for the outcome "thrombocytopenia" (severe AEs). This resulted in a hint of greater harm from carfilzomib + daratumumab + dexamethasone in comparison with carfilzomib + dexamethasone.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the probability and extent of the added benefit of the drug carfilzomib in combination with daratumumab and dexamethasone in comparison with the ACT is assessed as follows:

In summary, there are 1 positive and 2 negative effects of carfilzomib + daratumumab + dexamethasone compared with carfilzomib + dexamethasone in the category of side effects, each with the probability "hint".

Overall, there are only effects in individual specific AEs. In the outcome category of serious/severe side effects, there is essentially a hint of lesser harm with the extent "minor" for the outcome "renal and urinary disorders" and a hint of greater harm – also with the extent "minor" – for the outcome "thrombocytopenia". No usable analyses or data are available for the outcomes "discontinuation due to AEs" and "infusion-related reactions". In summary, an added benefit of carfilzomib + daratumumab + dexamethasone in comparison with carfilzomib + dexamethasone for adult patients with multiple myeloma who have received at least one prior therapy is not proven.

Table 3 shows a summary of probability and extent of the added benefit of carfilzomib + daratumumab + dexamethasone.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Carfilzomib + daratumumab + dexamethasone – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with multiple myeloma who have received at least one 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. 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**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is the assessment of the added benefit of carfilzomib in combination with daratumumab and dexamethasone (hereinafter "carfilzomib + daratumumab + dexamethasone") in comparison with the ACT in adult patients with multiple myeloma who have received at least one prior therapy.

The G-BA's specification of the ACT resulted in one research question, which is presented in the following Table 4.

Table 4: Research questions of the benefit assessment of carfilzomib + daratumumab + dexamethasone

Therapeutic indication	ACT[a]
Adult patients with multiple myeloma who have received at least one 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
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**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company chose carfilzomib in combination with dexamethasone (hereinafter "carfilzomib + dexamethasone") from the specified options as comparator therapy and thus followed the ACT defined by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on carfilzomib (status: 15 October 2020)
- bibliographical literature search on carfilzomib (last search on 15 October 2020)
- search in trial registries/trial results databases for studies on carfilzomib (last search on 15 October 2020)
- search on the G-BA website for carfilzomib (last search on 15 October 2020)

To check the completeness of the study pool:

- search in trial registries for studies on carfilzomib (last search on 22 January 2021)

The check did not identify any additional relevant studies.

2.3.1 Studies included

The study listed in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: carfilzomib + daratumumab + dexamethasone vs. carfilzomib + dexamethasone

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] yes/no [citation])
CANDOR	Yes	Yes	No	No[d]	Yes [3-5]	Yes [6,7]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Other sources: documents from the search on the G-BA website and other public sources.
d. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without access to the CSR in Module 5 of the dossier.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial; vs.: versus

The CANDOR study was used for the benefit assessment. The study pool concurs with that of the company.

2.3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: carfilzomib + daratumumab + dexamethasone vs. carfilzomib + dexamethasone

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
CANDOR	RCT[b], open-label, parallel	Adult patients (≥ 18 years) with relapsed or progressive multiple myeloma, with 1 to 3 prior lines of therapy[c], and ECOG PS of 0 to 2	Carfilzomib + daratumumab + dexamethasone (N = 312) Carfilzomib + dexamethasone (N = 154)	Screening[d]: ≤ 21 days Treatment: until disease progression, unacceptable toxicity, or treatment discontinuation following the physician's or patient's decision, for a maximum of 4 years Observation[e]: outcome-specific, at most until death, discontinuation of participation in the study or end of study First data cut-off: 14 July 2019[f] Second data cut-off: 15 June 2020[g]	102 study centres in Australia, Austria, Belgium, Bulgaria, Canada, Czech Republic, France, Greece, Hungary, Japan, Poland, Romania, Russia, South Korea, Spain, Taiwan, Turkey, United Kingdom, USA Period: 6/2017 – ongoing	Primary: progression-free survival Secondary: overall survival, health status, symptoms, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Randomization in a ratio of 2:1.
c. Induction therapy followed by stem cell transplantation and consolidation/maintenance therapy is considered as one line of therapy.
d. In case of exclusion, one rescreening possible at the physician's discretion.
e. Outcome-specific information is provided in Table 8.
f. First interim analysis for overall survival (planned after about 188 PFS events).
g. Second interim analysis for overall survival after about 36 months. The final analysis of overall survival is performed after 230 events or 58 months, whichever occurs earlier.

AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; N: number of randomized patients; PFS: progression-free survival; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the interventions – RCT, direct comparison: carfilzomib + daratumumab + dexamethasone vs. carfilzomib + dexamethasone (multipage table)

Study	Intervention	Comparison
CANDOR	Carfilzomib[a] ▪ cycle 1: 20 mg/m² body surface area[b] IV on days 1 and 2, then 56 mg/m² on days 8, 9, 15 and 16 ▪ from cycle 2: 56 mg/m² body surface area IV on days 1, 2, 8, 9, 15 and 16 + daratumumab[a] ▪ cycle 1: 8 mg/kg body weight IV on days 1 and 2, then 16 mg/kg body weight on days 8, 15 and 22 ▪ cycle 2: 16 mg/kg body weight IV on days 1, 8, 15 and 22 ▪ cycles 3−6: 16 mg/kg body weight IV on days 1 and 15 ▪ from cycle 7: 16 mg/kg body weight IV on day 1 + dexamethasone[a] all cycles: 20 mg IV on days 1 and 2, IV or PO on days 8, 9, 15 and 16, then 40 mg IV or PO on day 22 length of cycle: 28 days	Carfilzomib ▪ cycle 1: 20 mg/m² body surface area[b] IV on days 1 and 2, then 56 mg/m² on days 8, 9, 15 and 16 ▪ from cycle 2: 56 mg/m² body surface area IV on days 1, 2, 8, 9, 15 and 16 + dexamethasone ▪ all cycles 1: 20 mg IV on days 1 and 2, IV or PO on days 8, 9, 15 and 16, then 40 mg on day 22 length of cycle: 28 days
	Dose adjustments ▪ carfilzomib: dose adjustments, treatment interruptions or treatment discontinuation due to AEs ▪ daratumumab: dose adjustments for a change in body weight of ≥ 10% as well as dose delay, pause, or treatment discontinuation due to AEs ▪ dexamethasone: dose adjustments for age > 75 years and due to AEs; if carfilzomib therapy was discontinued, dexamethasone could be omitted at the discretion of the physician on days without daratumumab infusion; treatment discontinuation due to AEs possible	
	Pretreatment: ▪ pretreatment with carfilzomib or daratumumab was allowed under certain criteria (achievement of at least partial remission, no intolerance, no relapse within ≤ 60 days after treatment discontinuation, ≥ 6-month treatment-free interval) **Premedication before infusion** ▪ for carfilzomib ▫ prehydration in cycle 1 with 250 mL saline solution; prehydration was not required for patients in the intervention arm on days of daratumumab administration, however, prehydration could be administered at the investigator's discretion in cycle 1 on days 9 and 16 ▪ for daratumumab ▫ paracetamol PO or IV ▫ antihistamine (e.g. diphenhydramine) ▫ leukotriene inhibitor (e.g. montelukast)	

Table 7: Characteristics of the interventions – RCT, direct comparison: carfilzomib + daratumumab + dexamethasone vs. carfilzomib + dexamethasone (multipage table)

Study	Intervention	Comparison
	Permitted concomitant treatment ▪ antiviral prophylaxis (e.g. valaciclovir) ▪ hydration for prevention of myeloma-related kidney disease ▪ thrombosis prophylaxis (e.g. aspirin, low molecular weight heparin) ▪ tumour lysis syndrome prophylaxis with uric acid-lowering drugs (e.g. allopurinol) ▪ proton pump inhibitor (e.g. omeprazole) during dexamethasone therapy	
	Non-permitted concomitant treatment ▪ other anticancer therapies and radiation ▪ long-term corticosteroids for non-malignant conditions	
	Post-infusion treatment ▪ for daratumumab ▫ moderate- or long-acting corticosteroids[c] ▫ antihistamine[d] (e.g. diphenhydramine) ▫ leukotriene inhibitor[e] (e.g. montelukast) ▫ short-acting beta-2 agonist[d] (e.g. inhaled salbutamol) ▫ control medications for existing lung disease[d] (e.g. long-acting beta-2 agonists)	

a. On days when > 1 drug was administered, the order of administration was as follows: dexamethasone, premedication for daratumumab, carfilzomib, daratumumab, postmedication for daratumumab.
b. Maximum dose corresponds to the dose for 2.2 mg/m².
c. In the absence of infusion-related reactions after the first 3 infusions, post-infusion corticosteroids are administered per investigator discretion.
d. Mandatory post-infusion treatment for patients with a higher risk of respiratory complications.
AE: adverse event; IV: intravenous; PO: orally; RCT: randomized controlled trial; vs.: versus

The CANDOR study is an ongoing, open-label, randomized, active-controlled multicentre study on the comparison of carfilzomib + daratumumab + dexamethasone with carfilzomib + dexamethasone.

The study included adult patients with relapsed or progressive multiple myeloma after last treatment. The included patients had already received 1 to 3 prior lines of therapy. The inclusion of patients with relapse after previous therapy with carfilzomib or daratumumab was permitted under certain criteria, as was refractoriness to previous therapy with lenalidomide or a proteasome inhibitor (except carfilzomib). All patients had to have a general condition corresponding to an ECOG PS of 0 to 2.

312 patients were randomly assigned to treatment with carfilzomib + daratumumab + dexamethasone, and 154 to treatment with carfilzomib + dexamethasone. Randomization of the patients was in a 2:1 ratio and was stratified based on the following criteria: International Staging System (ISS) stage (1 or 2 versus 3), prior therapy with a proteasome inhibitor (yes versus no), number of prior lines of therapy (1 versus ≥ 2) and prior therapy with an antibody against cluster of differentiation 38 [CD38] antigen.

Treatment in both study arms was given in 28-day cycles until disease progression, unacceptable toxicity, withdrawal of consent or for a maximum of 4 years. The use of carfilzomib, daratumumab and dexamethasone in both study arms was largely in compliance with the requirements of the SPCs [8,9]. For dexamethasone, the SPC [8] recommends a dose reduction to 20 mg per week after the first week of treatment for patients aged ≥ 75 years. In the CANDOR study, > 75-year-olds received an additional 8 mg of dexamethasone on days 9 and 16 in the first cycle of therapy with carfilzomib + daratumumab + dexamethasone. In the comparator arm, however, the weekly dose of dexamethasone was reduced to 20 mg in all cycles for patients > 75 years of age. 8% of the patients in the intervention arm were > 75 years of age and were thus treated in deviation from the SPC. This has no impact on the present benefit assessment.

Primary outcome of the CANDOR study was PFS. Overall survival as well as outcomes on symptoms, health status, health-related quality of life and AEs were recorded as patient-relevant secondary and supplementary outcomes.

Data cut-offs

For the CANDOR study, the first data cut-off was planned after approximately 188 PFS events; a second and a third data cut-off for the analyses of overall survival were planned approximately 36 and 48 months after inclusion of the last patient. The final data cut-off is planned after the occurrence of about 230 deaths or 58 months after the inclusion of the last patient. With the current dossier, the company presented results on the following data cut-offs:

- first data cut-off from 14 July 2019 (planned after 188 PFS events)
- second data cut-off from 15 June 2020 (about 36 months after inclusion of the last patient)

The company based its conclusions primarily on the results of the first data cut-off (14 July 2019), but also partly used the results of the second data cut-off (15 June 2020) if it considered the differences between the results to be relevant. It did not provide a justification for this approach. Contrary to the approach of the company, only the planned second data cut-off was used as the longest available observation period for the present benefit assessment.

Treatment duration and follow-up observation

Table 8 shows the planned duration of follow-up observation of the patients for the individual outcomes.

Table 8: Planned duration of follow-up observation – RCT, direct comparison: carfilzomib + daratumumab + dexamethasone vs. carfilzomib + dexamethasone

Study **Outcome category** **Outcome**	**Planned follow-up observation**
CANDOR	
Mortality	
Overall survival	Until withdrawal of consent, lost to follow-up, death, or end of study
Morbidity	
Symptoms (EORTC QLQ-C30, EORTC QLQ-MY20), health status (EQ-5D VAS)	Until 30 (+ 3) days after the last dose of the study medication
Health-related quality of life	
EORTC QLQ-C30, EORTC QLQ-MY20	Until 30 (+ 3) days after the last dose of the study medication
Side effects	
All outcomes in the category of side effects	Until 30 days after the last study medication

EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma 20; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus

The observation periods for the outcomes of the categories of morbidity, health-related quality of life and side effects were systematically shortened because they were only recorded for the time period of treatment with the study medication (plus 30 days). 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 9 shows the characteristics of the patients in the study included.

Table 9: Characteristics of the study population – RCT, direct comparison: carfilzomib + daratumumab + dexamethasone vs. carfilzomib + dexamethasone (multipage table)

Study **Characteristic** **Category**	**Carfilzomib + daratumumab + dexamethasone** **N[a] = 312**	**Carfilzomib + dexamethasone** **N[a] = 154**
CANDOR		
Age [years], mean (SD)	63 (10)	64 (10)
Sex [F/M], %	43/57	41/59
ISS stage at baseline, n (%)		
I	147 (47)	79 (51)
II	103 (33)	48 (31)
III	61 (20)	27 (18)
Unknown	1 (< 1)	0 (0)
Time since first diagnosis [months], mean (SD)	47.9 (34.7)	44.0 (36.6)
Family origin, n (%)		
White	243 (78)	123 (80)
Asian	46 (15)	20 (13)
Black or African American	7 (2)	2 (1)
Other	16 (5)	9 (6)
ECOG PS, n (%)		
0 or 1	295 (95)	147 (95)
2	15 (5)	7 (5)
Missing	2 (< 1)	0 (0)
Cytogenetic risk group as determined by FISH, n (%)		
High	48 (15)	26 (17)
Standard	104 (33)	52 (34)
Unknown	160 (51)	76 (49)
Number of prior therapies, n (%)		
1	144 (46)	70 (46)
2	99 (32)	46 (30)
3	69 (22)	37 (24)
> 3	0 (0)	1 (1)
Prior therapies, n (%)		
Bortezomib or ixazomib	289 (93)	137 (89)
Lenalidomide	123 (39)	74 (48)
IMiD	206 (66)	110 (71)
Proteasome inhibitor	290 (93)	139 (90)
CD38 antibody	1 (< 1)	0 (0)

Table 9: Characteristics of the study population – RCT, direct comparison: carfilzomib + daratumumab + dexamethasone vs. carfilzomib + dexamethasone (multipage table)

Study Characteristic Category	**Carfilzomib + daratumumab + dexamethasone** **N[a] = 312**	**Carfilzomib + dexamethasone** **N[a] = 154**
Refractory to prior therapies, n (%)		
Bortezomib or ixazomib	100 (32)	55 (36)
Lenalidomide	99 (32)	55 (36)
IMiD	130 (42)	65 (42)
Proteasome inhibitor	102 (33)	55 (36)
Prior transplantation, n (%)		
Yes	195 (63)	75 (49)
No	117 (38)	79 (51)
Existing bone lesions, n (%)		
Yes	190 (61)	95 (62)
No	122 (39)	59 (38)
Multiple myeloma subtype, n (%)		
IgG	178 (57)	88 (57)
IgA	70 (22)	31 (20)
IgD	2 (< 1)	2 (1)
None	62 (20)	33 (21)
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)[b]	ND	ND

a. Number of randomized patients.
b. Study discontinuation at first data cut-off (14 July 2019), n (%): 20 (6.4) in the intervention arm vs. 11 (7.1) in the comparator arm.

CD38: cluster of differentiation 38; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; FISH: fluorescence in situ hybridization; IMiD: immunomodulatory drug; ISS: International Staging System; M: male; 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 are largely comparable between the study arms of the CANDOR study. The mean age of the included patients was 63 to 64 years, and just under 60% of them were male. About half of the patients had ISS stage I at baseline and about 19% had ISS stage III. The mean time from the initial diagnosis of disease progression or recurrence until study start was about 46 months. There were slight imbalances between the study arms with regard to prior therapy with lenalidomide: 48% of the patients in the carfilzomib + dexamethasone arm, and 39% of the patients in the carfilzomib + daratumumab + dexamethasone arm had already received prior therapy with this drug. Furthermore, more patients (63%) in the carfilzomib + daratumumab + dexamethasone arm had received a transplant than in the comparator arm (49%).

In both study arms, about 90% of the patients had received a proteasome inhibitor (mainly bortezomib or ixazomib) in one of the prior therapies. Overall, the disease was refractory to prior therapy with a proteasome inhibitor in about 1 third of the patients, although no information is available on this with regard to the last line of therapy. More than half of the patients had already received 2 or 3 prior therapies at the time of inclusion in the CANDOR study. Patients who were refractory to the proteasome inhibitor carfilzomib used in the study were excluded from participation in the study. The company did not provide any information on why a therapy with carfilzomib was suitable for approximately 1 third of the patients despite existing refractoriness to another proteasome inhibitor. The study showed at least no effect modification for the characteristic of refractoriness to a proteasome inhibitor (bortezomib or ixazomib).

Table 10 shows the mean and median treatment duration of the patients as well as the mean and median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: carfilzomib + daratumumab + dexamethasone vs. carfilzomib + daratumumab

Study **Duration of the study phase** **Outcome category**	**Carfilzomib + daratumumab + dexamethasone** **N = 312**	**Carfilzomib + dexamethasone** **N = 154**
CANDOR (second data cut-off [15 June 2020])		
Treatment duration [months][a]		
Median [min; max]	18.5 [0; 35]	9.4 [0; 33]
Mean (SD)	17.8 (10.9)	12.8 (10.2)
Observation period [months]		
Overall survival[b]		
Median [min; max]	27.3 [0; 34]	26.2 [0; 36]
Mean (SD)	22.7 (9.5)	21.6 (9.7)
Morbidity		
Symptoms (EORTC QLQ-C30)[c]		
Median [min; max]	19.6 [1; 35]	10.8 [1; 33]
Mean (SD)	17.9 (10.6)	13.8 (10.0)
Symptoms (EORTC QLQ-MY20)[c]		
Median [min; max]	19.6 [1; 35]	10.8 [1; 33]
Mean (SD)	17.9 (10.7)	13.8 (10.0)
Health status (EQ-5D VAS)[c]		
Median [min; max]	19.6 [1; 35]	10.9 [1; 33]
Mean (SD)	17.9 (10.7)	13.9 (10.0)
Health-related quality of life (EORTC QLQ-C30)[c]		
Median [min; max]	19.6 [1; 35]	10.8 [1; 33]
Mean (SD)	17.9 (10.6)	13.8 (10.0)
Health-related quality of life (EORTC QLQ-MY20)[c]		
Median [min; max]	19.6 [1; 35]	10.8 [1; 33]
Mean (SD)	17.9 (10.7)	13.8 (10.0)
Side effects[a]		
Median [min; max]	19.2 [0; 34]	10.3 [0; 33]
Mean (SD)	18.1 (10.5)	13.4 (9.8)

a. Data based on the safety population: N = 308 intervention vs. N = 153 comparator.
b. Calculated as time from randomization to time of last follow-up observation.
c. Deviating number of patients, the deviating values can be found in Table 16.

EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; max.: maximum; min: minimum; N: number of patients; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale; vs.: versus

The median treatment duration in the CANDOR study was about twice as long in the intervention arm as in the comparator arm (median: 18.5 vs. 9.4 months). Accordingly, the median observation periods of the outcomes on morbidity, health-related quality of life and side

effects in the intervention arm were about twice as long as in the comparator arm. Only the median observation period for overall survival is comparable between the 2 study arms.

Table 11 shows which subsequent therapies patients received after discontinuing the study medication.

Table 11: Information on subsequent antineoplastic therapies – RCT, direct comparison: carfilzomib + daratumumab + dexamethasone vs. carfilzomib + dexamethasone

Study Drug	Patients with subsequent therapy n (%)	
	Carfilzomib + daratumumab + dexamethasone N = 312	Carfilzomib + dexamethasone N = 154
CANDOR (first data cut-off [14 July 2019])		
Total	74 (23.7)	70 (45.5)
Dexamethasone	44 (14.1)	39 (25.3)
Lenalidomide	34 (10.9)	25 (16.2)
Pomalidomide	14 (4.5)	15 (9.7)
Daratumumab	4 (1.3)	24 (15.6)
Cyclophosphamide	19 (6.1)	8 (5.2)
Bortezomib	5 (1.6)	8 (5.2)
Etoposide	7 (2.2)	4 (2.6)
Doxorubicin	5 (1.6)	6 (3.9)
Cisplatin	6 (1.9)	4 (2.6)
Ixazomib	6 (1.9)	2 (1.3)
Dexamethasone/lenalidomide	6 (1.9)	1 (0.6)
Elotuzumab	5 (1.6)	2 (1.3)
Dexamethasone/pomalidomide	4 (1.3)	2 (1.3)
Thalidomide	4 (1.3)	2 (1.3)
Carfilzomib	3 (1.0)	3 (1.9)
Melphalan	2 (0.6)	4 (2.6)
Antineoplastic drugs	2 (0.6)	3 (1.9)
Bendamustine	2 (0.6)	3 (1.9)
Monoclonal antibodies	1 (0.3)	3 (1.9)
Isatuximab	0 (0)	2 (1.3)

n: number of patients in the category; N: number of analysed patients; RCT: randomized controlled trial; vs.: versus

In the CANDOR study, there were no restrictions regarding possible subsequent therapies.

The proportion of patients with at least one subsequent therapy at the first data cut-off (14 July 2019) was lower in the carfilzomib + daratumumab + dexamethasone arm than in the carfilzomib + dexamethasone arm (23.7% versus 45.5%). The type of subsequent therapies at

the first data cut-off was largely comparable in both study arms. The clearest difference is that, following treatment with carfilzomib + daratumumab + dexamethasone, only about 1% of the patients received subsequent therapy with daratumumab, whereas following treatment with carfilzomib + dexamethasone, about 16% of the patients received daratumumab.

No information on subsequent therapies is available for the second data cut-off (15 June 2020), which is the one relevant for the present benefit assessment.

Risk of bias across outcomes (study level)

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: carfilzomib + daratumumab + dexamethasone vs. carfilzomib + dexamethasone

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

The risk of bias across outcomes was rated as low for the CANDOR study. This concurs with the company's assessment.

Limitations resulting from the open-label study design are described in Section 2.4.2 with the outcome-specific risk of bias.

Transferability of the study results to the German health care context

The company stated that the results of the CANDOR study were transferable to the German health care context. The patient characteristics were comparable to the epidemiological data in Germany [10] and most study participants (66.5%) were from Europe. According to the company, there were no indications of biodynamic or kinetic differences between the individual population groups that could have an impact on the study results, particularly with regard to Germany.

The company did not provide any further information on the transferability of the study results to the German health care context.

2.4 Results on added benefit

2.4.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - symptoms measured with the EORTC QLQ-C30 symptom scales
  - symptoms measured with the EORTC QLQ-MY20 symptom scales
  - health status measured with the EQ-5D VAS
- Health-related quality of life
  - EORTC QLQ-C30, health-related quality of life scales
  - EORTC QLQ-MY20, health-related quality of life scales
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - infusion-related reactions
  - further specific AEs, if any

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

Table 13 shows for which outcomes data were available in the study included.

Table 13: Matrix of outcomes – RCT, direct comparison: carfilzomib + daratumumab + dexamethasone vs. carfilzomib + dexamethasone

Study	Outcomes										
	Overall survival	Symptoms (EORTC QLQ-C30)	Symptoms (EORTC QLQ-MY20)	EQ-5D VAS	Health-related quality of life (EORTC QLQ-C30)	Health-related quality of life (EORTC QLQ-MY20)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Infusion-related reactions	Further specific AEs[b]
CANDOR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[c]	No[c]	Yes

a. Operationalized as CTCAE grade ≥ 3.
b. The following events are considered (MedDRA coding): diarrhoea (PT, AEs), renal and urinary disorders (SOC, severe AEs [CTCAE grade ≥ 3]), thrombocytopenia (PT, severe AEs [CTCAE grade ≥ 3]).
c. No usable analyses or data available; for reasons, see Section 2.4.1.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; MedDRA: Medical Dictionary for Regulatory Activities; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma 20; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

Note on the responder analyses for the outcomes on symptoms and health-related quality of life

- In its dossier, the company presented responder analyses for the time to deterioration by 7 or 10 points for the outcome "health status" (EQ-5D VAS). These were not used for the dossier assessment. As explained in the *General Methods* of the Institute [1,11], for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to a predefined value of at least 15% of the scale range of an instrument (in post-hoc analyses exactly 15% of the scale range). The analyses of the mean change at the end of the study compared with the start of treatment were used for the present assessment. The responder analyses presented by the company are presented as supplementary information in Appendix C of the full dossier assessment.
- The company presented responder analyses for the time to deterioration by ≥ 10 points for both the EORTC QLQ-C30 and the EORTC QLQ-MY20 in its dossier. As explained in the *General Methods* of the Institute [1,11], for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to a predefined value of at least 15% of the scale range of an instrument (in post-hoc analyses exactly 15% of the scale range). Under certain conditions, a response threshold of 10 points for the scales of the EORTC QLQ-C30 in combination with an additional indication-specific module is

considered a sufficient approximation to an analysis with a 15% threshold (15 points) and is used for the benefit assessment (70% of the conclusions identical, difference of no more than one change step on the scale, see [12]). However, this does not apply to the EORTC QLQ-C30 in combination with the EORTC QLQ-MY20. The analyses of the mean change at the end of the study compared with the start of treatment were used for the present assessment.

The responder analyses with the response threshold of 10 points provided by the company are presented as supplementary information in Appendix C of the full dossier assessment.

- Overall, it should be noted that the company did not provide any information on which exact statistical models it used for the above-mentioned responder analyses.

Notes on side effects

No usable data are available for the following patient-relevant outcomes:

- Discontinuation due to AEs: For the outcome "discontinuation due to AEs", the company provided analyses of the odds ratio, the relative risk (RR) and the absolute risk reduction; analyses of the hazard ratio (HR) are missing. Due to the marked differences in the observation periods between the treatment arms, the responder analyses presented by the company cannot be used as a substitute for the missing event time analyses (HR).
- Infusion-related reactions: The company presented different operationalizations for the outcome "infusion-related reactions":
  - infusion related reactions (Preferred Term [PT], AEs) – referred to by the company as "infusion-related reactions"
  - infusion reaction (Amgen Medical Dictionary for Regulatory Activities [MedDRA] Query [AMQ, narrow scope]) for carfilzomib: analyses each for AEs, SAEs, and severe AEs on the event on the same day of any carfilzomib dose and event on the same day of the first carfilzomib dose
  - daratumumab-related infusion reactions (AMQ [narrow scope]) for daratumumab: analyses each for AEs, SAEs and severe UEs on the event on the same or next day of a daratumumab dose and event on the same or next day of the first daratumumab dose

  When considering the different operationalizations, it is remarkable that the AMQs presented by the company showed notably higher event rates than the PT infusion-related reactions (e.g. infusion reaction on the same day of any carfilzomib dose [AEs for carfilzomib]: 139 [45.1%] versus 48 [31.4%]; infusion related reactions [PT, AEs]: 25 [8.1%] versus 3 [2.0%]). There is no precise information on the operationalization for any of the analyses presented by the company for the outcome "infusion-related reactions": For example, it remains unclear which individual PTs were included in the analyses of the AMQs and in which way the PT was recorded (e.g. the time period within which an AE had to occur in order to be included in the analysis). Thus, it is not comprehensible what caused the differences in the results. Furthermore, for its analyses of AMQs, the company

only presented analyses in which the events that occurred were assigned to the individual drugs carfilzomib and daratumumab. For a meaningful interpretation of the results, however, an analysis of the total events that occurred in the study arms is necessary. In summary, for the reasons mentioned above, no usable data are available for any of the operationalizations presented by the company for the outcome "infusion-related reactions".

2.4.2 Risk of bias

Table 14 describes the risk of bias for the results of the relevant outcomes.

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: carfilzomib + daratumumab + dexamethasone vs. carfilzomib + dexamethasone

Study		Outcomes										
	Study level	Overall survival	Symptoms (EORTC QLQ-C30)	Symptoms (EORTC QLQ-MY20)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	Health-related quality of life (EORTC QLQ-MY20)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Infusion-related reactions	Further specific AEs[b]
CANDOR	L	L	H[c, d, e]	H[c, d, e]	H[c, d, e]	H[c, d, e]	H[c, d, e]	H[f]	H[f]	–[g]	–[g]	H[e, f]

a. Operationalized as CTCAE grade ≥ 3.
b. The following events are considered (MedDRA coding): diarrhoea (PT, AEs), renal and urinary disorders (SOC, severe AEs [CTCAE grade ≥ 3]), thrombocytopenia (PT, severe AEs [CTCAE grade ≥ 3]).
c.: Large proportion of patients (> 10%) not considered in the analysis.
d. Strong decrease in responses over the course of the study, which differ notably between the treatment arms (> 10% points)
e. Lack of blinding in subjective recording of outcomes (in the case of AEs, this aspect only concerns non-serious/non-severe AEs).
f. Differences in observation periods between treatment groups for potentially informative reasons.
g. No usable analysis or data available; for reasons, see Section 2.4.1.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma 20; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

The risk of bias for the results of the outcome "overall survival" was rated as low. This concurs with the company's assessment.

Due to the high proportion of patients not included in the analysis, the strong decrease in response rates over the course of the study and the different response rates between the

treatment arms, as well as the lack of blinding in subjective recording of outcomes, the risk of bias was rated as high for the results of the symptom outcomes (symptom scales of the EORTC QLQ-C30 and the EORTC QLQ-MY20), health-related quality of life (health-related quality of life scales of the EORTC QLQ-C30 and the EORTC QLQ-MY20) and health status (EQ-5D VAS). The company also rated the risk of bias of these outcomes as high, which it justified exclusively with the lack of blinding in subjective recording of outcomes due to the patients' self-assessment.

Due to different observation periods between the treatment groups for potentially informative reasons, the risk of bias was rated as high for the results of the following outcomes: SAEs, severe AEs, as well as diarrhoea (PT, AEs), renal and urinary disorders (System Organ Class [SOC], severe AEs [CTCAE grade ≥ 3]) and thrombocytopenia (PT, severe AEs). For the results of the non-serious/non-severe AE "diarrhoea", the lack of blinding in subjective recording of outcomes additionally contributed to the high risk of bias. No usable data are available for the outcomes "discontinuation due to AEs" and "infusion-related reactions". For the results of the outcomes "SAEs", "severe AEs", as well as "renal and urinary disorders" (severe AEs) and "thrombocytopenia" (severe AEs), the assessment of the risk of bias deviates from that of the company, which assumed a low risk of bias for all serious/severe AEs. For diarrhoea (AEs), the assessment of the risk of bias corresponds to that of the company, which also assumed a high risk of bias due to the lack of blinding.

2.4.3 Results

Table 15 and Table 16 summarize the results for the comparison of carfilzomib + daratumumab + dexamethasone with carfilzomib + dexamethasone in patients with multiple myeloma who have received at least one prior therapy.

Kaplan-Meier curves for event time analyses can be found in Appendix A, results for common AEs in Appendix B of the full dossier assessment.

Table 15: Results (mortality, side effects) – 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
CANDOR					
Mortality					
Overall survival	312	NA 89 (28.5)	154	33.2 [33.2; NC] 51 (33.1)	0.76 [0.54; 1.07]; 0.118[a]
Side effects					
AEs (supplementary information)[b]	308	0.3 [0.2; 0.3] 307 (99.7)	153	0.5 [0.3; 0.5] 148 (96.7)	–
SAEs[b]	308	10.4 [8.5; 13.7] 192 (62.3)	153	13.2 [7.6; 28.7] 75 (49.0)	1.16 [0.89; 1.51]; 0.279[c]
Severe AEs[b, d]	308	1.7 [1.1; 2.5] 267 (86.7)	153	2.6 [1.9; 3.5] 116 (75.8)	1.22 [0.98; 1.51]; 0.080[c]
Discontinuation due to AEs	308	ND 85 (27.6)	153	ND 38 (24.8)	ND[e]
Infusion-related reactions	No usable data available[f]				
Diarrhoea (PT, AEs)	308	NA [22.5; NC] 110 (35.7)	153	NA 26 (17.0)	2.02 [1.32; 3.09]; 0.001[c]
Renal and urinary disorders (SOC, severe AEs[d])	308	NA 15 (4.9)	153	NA 14 (9.2)	0.47 [0.23; 0.98]; 0.040[c]
Thrombocytopenia (PT, severe AEs[d])	308	NA 76 (24.7)	153	NA 25 (16.3)	1.57 [1.00; 2.47]; 0.049[c]

a. HR and 95% CI from stratified Cox model; 2-sided p-value from stratified log-rank test; stratified by randomization factors.
b. Overall rate without AEs attributed to progression of the underlying disease, defined as the PTs "plasma cell myeloma" (referred to as "multiple myeloma" by the company) and "plasmocytoma".
c. No information on the model used, 2-sided p-value from unstratified log-rank test.
d. Operationalized as CTCAE grade ≥ 3.
e. The company did not present any analyses on the HR; data on the RR cannot be used due to the large differences in observation periods.
f. See Section 2.4.1 for reasons.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Table 16: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: carfilzomib + daratumumab + dexamethasone vs. carfilzomib + daratumumab + dexamethasone

Study Outcome category Outcome	Carfilzomib + daratumumab + dexamethasone			Carfilzomib + dexamethasone			Carfilzomib + daratumumab + dexamethasone vs. carfilzomib + dexamethasone
	N[a]	Values at baseline mean (SD)	Change at end of study mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change at end of study mean[b] (SE)	MD [95% CI]; p-value[b]
CANDOR							
Morbidity							
Symptoms (EORTC QLQ-C30)[c]							
Fatigue	281	31.5 (24.19)	2.8 (0.90)	128	29.1 (23.46)	2.6 (1.43)	0.1 [−3.19; 3.45]; 0.939
Nausea and vomiting	281	3.2 (10.62)	1.6 (0.28)	128	2.1 (7.25)	0.7 (0.56)	0.9 [−0.31; 2.14]; 0.142
Pain	281	29.6 (28.43)	−3.0 (0.94)	128	25.8 (27.34)	−2.7 (1.50)	−0.2 [−3.70; 3.25]; 0.897
Dyspnoea	281	12.6 (20.51)	8.2 (1.00)	128	12.5 (20.06)	11.4 (1.61)	−3.3 [−6.97; 0.47]; 0.086
Insomnia	281	19.3 (26.16)	4.5 (1.10)	128	17.7 (27.09)	2.3 (1.76)	2.3 [−1.81; 6.36]; 0.275
Appetite loss	281	11.4 (20.43)	−0.7 (0.46)	128	7.3 (19.14)	0.6 (0.86)	−1.3 [−3.18; 0.68]; 0.204
Constipation	281	11.2 (22.41)	−1.5 (0.81)	128	5.5 (14.36)	−2.3 (1.28)	0.8 [−2.17; 3.82]; 0.589
Diarrhoea	281	6.2 (15.98)	3.3 (0.75)	128	4.7 (13.05)	2.8 (1.25)	0.5 [−2.38; 3.35]; 0.741
Symptoms (EORTC QLQ-MY20)[c]							
Disease-related symptoms	278	77.3 (19.58)	3.8 (0.68)	128	78.6 (19.97)	3.1 (0.99)	0.7 [−1.51; 2.99]; 0.517
Side effects	278	85.8 (13.17)	−3.3 (0.57)	128	88.8 (11.87)	−2.6 (0.82)	−0.7 [−2.56; 1.22]; 0.488
Health status (EQ-5D VAS)[d]	278	67.26 (18.88)	−0.33 (0.73)	127	72.93 (16.64)	−0.93 (1.06)	0.60 [−1.85; 3.05]; 0.632
Health-related quality of life							
EORTC QLQ-C30[d]							
Global health status	281	61.9 (20.12)	0.3 (0.74)	128	66.9 (17.73)	−0.4 (1.18)	0.6 [−2.11; 3.37]; 0.652
Physical functioning	281	76.8 (21.73)	−2.3 (0.74)	128	82.2 (17.19)	−3.4 (1.15)	1.0 [−1.67; 3.73]; 0.454
Role functioning	281	75.3 (27.43)	−4.5 (1.03)	128	78.3 (27.15)	−6.6 (1.62)	2.1 [−1.65; 5.90]; 0.269

Table 16: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: carfilzomib + daratumumab + dexamethasone vs. carfilzomib + daratumumab + dexamethasone

Study Outcome category Outcome	Carfilzomib + daratumumab + dexamethasone			Carfilzomib + dexamethasone			Carfilzomib + daratumumab + dexamethasone vs. carfilzomib + dexamethasone
	N[a]	Values at baseline mean (SD)	Change at end of study mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change at end of study mean[b] (SE)	MD [95% CI]; p-value[b]
Emotional functioning	281	81.3 (19.64)	−0.2 (0.75)	128	82.1 (16.67)	0.1 (1.18)	−0.3 [−3.03; 2.45]; 0.836
Cognitive functioning	281	85.8 (17.81)	−4.0 (0.77)	128	87.6 (17.15)	−3.2 (1.22)	−0.8 [−3.62; 2.06]; 0.590
Social functioning	281	77.9 (26.83)	−4.5 (0.95)	128	83.2 (23.71)	−6.2 (1.50)	1.7 [−1.77; 5.22]; 0.334
EORTC QLQ-MY20[d]							
Body image	278	81.4 (27.21)	−2.0 (1.15)	128	86.5 (20.25)	−2.7 (1.67)	0.7 [−3.18; 4.50]; 0.735
Future perspective	278	66.0 (26.55)	7.3 (0.94)	128	67.1 (26.47)	6.7 (1.37)	0.6 [−2.52; 3.69]; 0.710

a. Number of patients considered in the analysis for the calculation of the effect estimation; the values at baseline may be based on other patient numbers.
b. MMRM with time and treatment as independent variables and baseline value as covariate.
c. Lower (decreasing) values indicate better symptoms; negative effects (intervention minus control) indicate an advantage for the intervention.
d. Higher (increasing) values indicate better health status or better quality of life; positive effects (intervention minus control) indicate an advantage for the intervention.

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma 20; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; vs.: versus

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

The company based its conclusions on the outcomes primarily on the results of the first data cut-off (14 July 2019), but also partly used the results of the second data cut-off (15 June 2020) if it considered the differences between the results to be relevant. It did not provide a justification for its approach. In this report, all conclusions refer to the results at the second data cut-off (15 June 2020).

Mortality

Overall survival

The CANDOR study showed no statistically significant difference between the treatment groups for the outcome "overall survival". This resulted in no hint of an added benefit of carfilzomib + daratumumab + dexamethasone in comparison with carfilzomib + dexamethasone; an added benefit is therefore not proven.

This deviates from the assessment of the company, which claimed an indication of an added benefit for the outcome "overall survival". The company based this assessment on a meta-analysis of the studies CANDOR and CASTOR (daratumumab + bortezomib + dexamethasone versus bortezomib + dexamethasone). Since the CASTOR study did not investigate the intervention relevant to the present benefit assessment (carfilzomib + daratumumab + dexamethasone), the CASTOR study and thus the meta-analysis presented by the company for the outcome "overall survival" are not relevant to the present benefit assessment.

Morbidity

Symptoms (EORTC QLQ-C30)

For the symptom outcomes, recorded with the EORTC QLQ-C30, the analyses of the mean change at the end of the study compared with the start of treatment over the entire course of the study were used in the present benefit assessment. There were no statistically significant differences between the treatment groups in any of the EORTC QLQ-C30 symptom scales (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea). In each case, this resulted in no hint of an added benefit of carfilzomib + daratumumab + dexamethasone in comparison with carfilzomib + dexamethasone; an added benefit is therefore not proven.

This corresponds to the assessment of the company insofar as the company used the results of the responder analyses for the EORTC QLQ-C30 questionnaire, but also derived no added benefit across outcomes for the symptoms (EORTC QLQ-C30).

Symptoms (EORTC QLQ-MY20)

For the symptom outcomes, recorded with the EORTC QLQ-MY20, the analyses of the mean change at the end of the study compared with the start of treatment over the entire course of the study were used in the present benefit assessment. There were no statistically significant differences between the treatment groups in any of the EORTC QLQ-MY20 symptom scales (disease-related symptoms, side effects). In each case, this resulted in no hint of an added benefit of carfilzomib + daratumumab + dexamethasone in comparison with carfilzomib + dexamethasone; an added benefit is therefore not proven.

This deviates from the assessment of the company, which used the results of the responder analyses for the EORTC QLQ-MY20 questionnaire and assigned the entire EORTC

QLQ-MY20 questionnaire to health-related quality of life. In doing so, it derived a hint of an added benefit across outcomes for health-related quality of life.

Health status (EQ-5D VAS)

The outcome "health status" was recorded in the CANDOR study with the EQ-5D VAS. The analysis of the mean change at the end of the study compared with the start of treatment over the entire course of the study was used in the present benefit assessment. There was no statistically significant difference between the treatment groups. This resulted in no hint of an added benefit of carfilzomib + daratumumab + dexamethasone in comparison with carfilzomib + dexamethasone; an added benefit is therefore not proven.

This deviates from the assessment of the company, which used the results of the responder analyses for health status (EQ-5D VAS) and derived a hint of an added benefit from it.

Health-related quality of life

EORTC QLQ-C30

For the outcome "health-related quality of life", recorded with the EORTC QLQ-C30, the analyses of the mean change at the end of the study compared with the start of treatment over the entire course of the study were used in the present benefit assessment. There were no statistically significant differences between the treatment groups in any of the EORTC QLQ-C30 scales on health-related quality of life (global health status, physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning). In each case, this resulted in no hint of an added benefit of carfilzomib + daratumumab + dexamethasone in comparison with carfilzomib + dexamethasone; an added benefit is therefore not proven.

This deviates from the assessment of the company, which used the results of the responder analyses for the EORTC QLQ-C30 questionnaire and derived a hint of an added benefit across outcomes for the outcome category "health-related quality of life".

EORTC QLQ-MY20

For the outcome "health-related quality of life", recorded with the EORTC QLQ-MY20, the analyses of the mean change at the end of the study compared with the start of treatment over the entire course of the study were used in the present benefit assessment. There were no statistically significant differences between the treatment groups in any of the EORTC QLQ-MY20 scales on health-related quality of life (body image, future perspective). In each case, this resulted in no hint of an added benefit of carfilzomib + daratumumab + dexamethasone in comparison with carfilzomib + dexamethasone; an added benefit is therefore not proven.

This deviates from the assessment of the company, which used the results of the responder analyses for the EORTC QLQ-MY20 questionnaire and derived a hint of an added benefit across outcomes for the outcome category "health-related quality of life".

Side effects

SAEs, severe AEs

There was no statistically significant difference between the treatment groups for the outcomes "SAEs" and "severe AEs". In each case, this resulted in no hint of greater or lesser harm from carfilzomib + daratumumab + dexamethasone in comparison with carfilzomib + dexamethasone; greater or lesser harm is therefore not proven.

This corresponds to the assessment of the company insofar as the company did not derive an indication of a greater risk of harm across outcomes for the outcome category "side effects".

Discontinuation due to AEs

No usable data are available for discontinuation due to AEs (see Section 2.4.1 for reasons). This resulted in no hint of greater or lesser harm from carfilzomib + daratumumab + dexamethasone in comparison with carfilzomib + dexamethasone; greater or lesser harm is therefore not proven.

This deviates from the assessment of the company insofar as the company used the results of the RR for discontinuation due to AEs and overall derived no indication of a greater risk of harm for the outcome category of side effects.

Infusion-related reactions

No usable data are available for infusion-related reactions (see Section 2.4.1 for reasons). This resulted in no hint of greater or lesser harm from carfilzomib + daratumumab + dexamethasone in comparison with carfilzomib + dexamethasone; greater or lesser harm is therefore not proven.

This deviates from the assessment of the company insofar as the company used the results of different operationalizations (see Section 2.4.1) for the outcome "infusion-related reactions" and overall derived no indication of a greater risk of harm for the outcome category of side effects.

Diarrhoea (AEs)

A statistically significant difference to the disadvantage of carfilzomib + daratumumab + dexamethasone was shown for the outcome "diarrhoea" (AEs). This resulted in a hint of greater harm from carfilzomib + daratumumab + dexamethasone in comparison with carfilzomib + dexamethasone.

This deviates from the assessment of the company insofar as the company did not derive an indication of a greater risk of harm across outcomes for the outcome category "side effects".

Renal and urinary disorders (severe AEs)

A statistically significant difference in favour of carfilzomib + daratumumab + dexamethasone was shown for the outcome "renal and urinary disorders" (severe AEs). This resulted in a hint of lesser harm from carfilzomib + daratumumab + dexamethasone in comparison with carfilzomib + dexamethasone.

This deviates from the assessment of the company insofar as the company did not derive an indication of a greater risk of harm across outcomes for the outcome category "side effects".

Thrombocytopenia (severe AEs)

A statistically significant difference to the disadvantage of carfilzomib + daratumumab + dexamethasone was shown for the outcome "thrombocytopenia" (severe AEs). This resulted in a hint of greater harm from carfilzomib + daratumumab + dexamethasone in comparison with carfilzomib + dexamethasone.

This deviates from the assessment of the company insofar as the company did not derive an indication of a greater risk of harm across outcomes for the outcome category "side effects".

2.4.4 Subgroups and other effect modifiers

The following potential effect modifiers were considered for the present assessment:

- sex (female/male)
- age (≤ 75 years/> 75 years)
- ISS stage at baseline (I or II/III)

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. Moreover, for binary data, there had to be 10 events in at least one subgroup.

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 subgroup analyses for the continuous analyses of the outcomes on symptoms and health-related quality of life (each recorded with the EORTC QLQ-MY20 scales) as well as on health status (EQ-5D VAS). For the presented subgroup analyses on symptoms and health-related quality of life (each recorded with the EORTC QLQ-C30), the interaction p-values presented by the company do not correspond to the effect estimations (mean difference [MD] and respective 95% confidence interval [CI]) within the subgroup characteristics. Therefore, an assessment of a possible effect modification based on these p-values was not possible. Nevertheless, the subgroup analyses provided by the company allowed the conclusion that there were no relevant effect modifications due to the characteristics considered.

Overall, no relevant effect modifications by age, sex or ISS stage at baseline were identified for any of the patient-relevant outcomes according to the methods described.

2.5 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 17).

Table 17: Extent of added benefit at outcome level: carfilzomib + daratumumab + dexamethasone vs. carfilzomib + dexamethasone (multipage table)

Outcome category **Outcome**	**Carfilzomib + daratumumab + dexamethasone vs. carfilzomib + dexamethasone** **Median time to event (months) or change at end of study (mean)** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
Overall survival	Median: NA vs. 33.2 HR: 0.76 [0.54; 1.07]; p = 0.118	Lesser benefit/added benefit not proven
Morbidity		
Symptoms (EORTC QLQ-C30)		
Fatigue	2.8 vs. 2.6 MD: 0.1 [−3.19; 3.45]; p = 0.939	Lesser benefit/added benefit not proven
Nausea and vomiting	1.6 vs. 0.7 MD: 0.9 [−0.31; 2.14]; p = 0.142	Lesser benefit/added benefit not proven
Pain	−3.0 vs. −2.7 MD: −0.2 [−3.70; 3.25]; p = 0.897	Lesser benefit/added benefit not proven
Dyspnoea	8.2 vs. 11.4 MD: −3.3 [−6.97; 0.47]; p = 0.086	Lesser benefit/added benefit not proven
Insomnia	4.5 vs. 2.3 MD: 2.3 [−1.81; 6.36]; p = 0.275	Lesser benefit/added benefit not proven
Appetite loss	−0.7 vs. 0.6 MD: −1.3 [−3.18; 0.68]; p = 0.204	Lesser benefit/added benefit not proven
Constipation	−1.5 vs. −2.3 MD: 0.8 [−2.17; 3.82]; p = 0.589	Lesser benefit/added benefit not proven
Diarrhoea	3.3 vs. 2.8 MD: 0.5 [−2.38; 3.35]; p = 0.741	Lesser benefit/added benefit not proven

Table 17: Extent of added benefit at outcome level: carfilzomib + daratumumab + dexamethasone vs. carfilzomib + dexamethasone (multipage table)

Outcome category **Outcome**	**Carfilzomib + daratumumab + dexamethasone vs. carfilzomib + dexamethasone** **Median time to event (months) or change at end of study (mean)** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Symptoms (EORTC QLQ-MY20)		
Disease-related symptoms	3.8 vs. 3.1 MD: 0.7 [−1.51; 2.99]; p = 0.517	Lesser benefit/added benefit not proven
Side effects	−3.3 vs. −2.6 MD: −0.7 [−2.56; 1.22]; p = 0.488	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	−0.33 vs. −0.93 MD: 0.60 [−1.85; 3.05]; p = 0.632	Lesser benefit/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30		
Global health status	0.3 vs. −0.4 MD: 0.6 [−2.11; 3.37]; p = 0.652	Lesser benefit/added benefit not proven
Physical functioning	−2.3 vs. −3.4 MD: 1.0 [−1.67; 3.73]; p = 0.454	Lesser benefit/added benefit not proven
Role functioning	−4.5 vs. −6.6 MD: 2.1 [−1.65; 5.90]; p = 0.269	Lesser benefit/added benefit not proven
Emotional functioning	−0.2 vs. 0.1 MD: −0.3 [−3.03; 2.45]; p = 0.836	Lesser benefit/added benefit not proven
Cognitive functioning	−4.0 vs. −3.2 MD: −0.8 [−3.62; 2.06]; p = 0.590	Lesser benefit/added benefit not proven
Social functioning	−4.5 vs. −6.2 MD: 1.7 [−1.77; 5.22]; p = 0.334	Lesser benefit/added benefit not proven

Table 17: Extent of added benefit at outcome level: carfilzomib + daratumumab + dexamethasone vs. carfilzomib + dexamethasone (multipage table)

Outcome category **Outcome**	**Carfilzomib + daratumumab + dexamethasone vs. carfilzomib + dexamethasone** **Median time to event (months) or change at end of study (mean)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
EORTC QLQ-MY20		
Body image	−2.0 vs. −2.7 MD: 0.7 [−3.18; 4.50]; p = 0.735	Lesser benefit/added benefit not proven
Future perspective	7.3 vs. 6.7 MD: 0.6 [−2.52; 3.69]; p = 0.710	Lesser benefit/added benefit not proven
Side effects		
SAEs	Median: 10.4 vs. 13.2 HR: 1.16 [0.89; 1.51]; p = 0.279	Lesser benefit/added benefit not proven
Severe AEs	Median: 1.7 vs. 2.6 HR: 1.22 [0.98; 1.51]; p = 0.080	Lesser benefit/added benefit not proven
Discontinuation due to AEs	No usable analysis available[c]	Lesser benefit/added benefit not proven
Infusion-related reactions	No usable data available[c]	Lesser benefit/added benefit not proven
Diarrhoea (AEs)	Median: NA vs. NA HR: 2.02 [1.32; 3.09] HR: 0.50 [0.32; 0.76][d]; p = 0.001 probability: “hint”	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: “considerable”
Renal and urinary disorders (severe AEs)	Median: NA vs. NA HR: 0.47 [0.23; 0.98]; p = 0.040 probability: “hint”	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ lesser harm, extent: “minor”
Thrombocytopenia (severe AEs)	Median: NA vs. NA HR: 1.57 [1.00; 2.47] HR: 0.64 [0.40; 1.00][d]; p = 0.049 probability: “hint”	Outcome category: serious/severe side effects Greater harm, extent: “minor“[e]

Table 17: Extent of added benefit at outcome level: carfilzomib + daratumumab + dexamethasone vs. carfilzomib + dexamethasone (multipage table)

Outcome category **Outcome**	**Carfilzomib + daratumumab + dexamethasone vs. carfilzomib + dexamethasone** **Median time to event (months) or change at end of study (mean)** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
a. Probability provided if there is a statistically significant and relevant effect. b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u). c. See Section 2.4.1 for reasons. d. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit. e. Derivation is via p-value, effect cannot be more than "minor". AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; MD: mean difference; NA: not achieved; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma 20; SAE: serious adverse event; VAS: visual analogue scale		

2.5.2 Overall conclusion on added benefit

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

Table 18: Positive and negative effects from the assessment of carfilzomib + daratumumab + dexamethasone in comparison with carfilzomib + dexamethasone

Positive effects	**Negative effects**
–	Non-serious/non-severe side effects ▪ diarrhoea: hint of greater harm – extent: "considerable"
Serious/severe side effects ▪ renal and urinary disorders (severe AEs): hint of lesser harm – extent: "minor"	Serious/severe side effects ▪ thrombocytopenia (severe AEs): hint of greater harm – extent: "minor"
No usable analyses or data are available for the outcomes "discontinuation due to AEs" and "infusion-related reactions". AE: adverse event	

In summary, there are 1 positive and 2 negative effects of carfilzomib + daratumumab + dexamethasone compared with carfilzomib + dexamethasone in the category of side effects, each with the probability "hint".

Overall, there are only effects in individual specific AEs. In the outcome category of serious/severe side effects, there is essentially a hint of lesser harm with the extent "minor" for

the outcome “renal and urinary disorders” and a hint of greater harm – also with the extent “minor” – for the outcome “thrombocytopenia”. No usable analyses or data are available for the outcomes “discontinuation due to AEs” and “infusion-related reactions”. In summary, an added benefit of carfilzomib + daratumumab + dexamethasone in comparison with carfilzomib + dexamethasone for adult patients with multiple myeloma who have received at least one prior therapy is not proven.

The result of the assessment of the added benefit of carfilzomib + daratumumab + dexamethasone in comparison with the ACT is summarized in Table 19.

Table 19: Carfilzomib + daratumumab + dexamethasone – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with multiple myeloma who have received at least one 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. 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**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The assessment described above deviates from that of the company, which claimed an indication of a minor added benefit.

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

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Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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The full report (German version) is published under https://www.iqwig.de/en/projects/a21-08.html.