IQWiG Reports – Commission No. A21-60

Isatuximab (multiple myeloma, after ≥ 1 prior therapy) –

Benefit assessment according to §35a Social Code Book V[1] (early benefit assessment)

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Isatuximab (multiples Myelom, nach ≥ 1 Vortherapie) – Nutzenbewertung gemäß § 35a SGB V (frühe Nutzenbewertung)* (Version 1.0; Status: 12 August 2021). Please note: This document was translated by an external translator and 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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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

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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
CD38	cluster of differentiation 38
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
ECOG-PS	Eastern Cooperative Oncology Group – Performance Status
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D VAS	European Quality of Life Questionnaire – 5 Dimensions visual analogue scale
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
M-protein	monoclonal protein
PFS	progression-free survival
PT	preferred term
QLQ-C30	Quality of Life Questionnaire – Core 30
QLQ-MY20	Quality of Life Questionnaire – Multiple Myeloma 20
RCT	randomized controlled trial
R-ISS	Revised International Staging System
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
TEAE	treatment emergent adverse events

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 isatuximab in combination with carfilzomib and dexamethasone. 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 12 May 2021.

Research question

The aim of this report is to assess the added benefit of isatuximab in combination with carfilzomib and dexamethasone (hereinafter isatuximab + carfilzomib + dexamethasone) in comparison with the appropriate comparator therapy (ACT) in adult patients with multiple myeloma who have received at least 1 prior therapy.

The G-BA's specification of the ACT results in the research question presented in Table 2.

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

Indication	**ACT**[a]
Adult patients with multiple myeloma who have received at least 1 prior therapy[b]	▪ 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. 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**. b. As per the G-BA, it is assumed that high-dose chemotherapy with stem cell transplantation is not an option for the patients at the time of the current therapy. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA's specification of the ACT. To this effect, instead of explicitly selecting a drug combination from the identified options, the company included a study comparing isatuximab in combination with carfilzomib and dexamethasone versus carfilzomib in combination with dexamethasone.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier. RCTs were used for the derivation of added benefit.

Study pool and study design

The IKEMA study was included for the benefit assessment.

IKEMA is an ongoing, open-label, randomized, multicentric study comparing isatuximab + carfilzomib + dexamethasone versus carfilzomib + dexamethasone.

The study included adult patients with relapsed and/or refractory multiple myeloma who had already received 1 to 3 prior therapies and had measurable disease in the form of an elevated monoclonal protein (M-protein) concentration (≥ 0.5 g/dL in serum or ≥ 200 mg/24 h in urine).

Prior treatment with a CD38 antibody was allowed with some restrictions. The study excluded patients with primary refractory myeloma, prior carfilzomib therapy as well as patients whose general condition corresponded to an Eastern Cooperative Oncology Group – Performance Status (ECOG-PS) > 2; therefore, no data were available on these patients.

A total of 302 patients were randomly allocated in a 3:2 ratio to treatment with isatuximab + carfilzomib + dexamethasone (N = 179) or treatment with carfilzomib + dexamethasone (N = 123). Stratification factors were disease stage in accordance with the Revised International Staging System (R-ISS) (I or II versus III versus not classified) as well as the number of prior treatment lines (1 versus > 1).

The study medication was largely in accordance with the specifications of the Summary of Product Characteristics (SPC).

Primary outcome of the IKEMA study was progression-free survival (PFS). As patient-relevant secondary outcomes, overall survival as well as morbidity, health-related quality of life, and adverse events (AEs) outcomes were surveyed.

The dossier provides data on an interim data cut-off which also served as the basis of approval. This cut-off was predefined and applied after 65% of 159 PFS events had occurred. The final analysis of the overall survival outcome is to take place 3 years after the cut-off for primary PFS.

Risk of bias

The risk of bias across outcomes is rated as low for the IKEMA study.

On the outcome level, the risk of bias is deemed low for the results of overall survival, serious adverse events (SAEs), and severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3). For the results of all other outcomes, the risk of bias is considered high.

Due to discontinuation of observation for potentially informative reasons, there is a high risk of bias for the results of the morbidity, health-related quality of life, and specific AEs outcomes. Further, there is a high risk of bias because patients' subjective evaluations were surveyed via questionnaires in an open-label study.

Hence, for the outcomes of overall survival and SAEs, at most an indication can be derived, and for each of the other outcomes, at most hints, e.g. of added benefit. Due to the operationalization used, only a hint can be derived for severe AEs.

Results

Mortality

Overall survival

For the outcome of overall survival, the IKEMA study fails to show a statistically significant difference between treatment groups. Consequently, there is no hint of added benefit of isatuximab + carfilzomib + dexamethasone in comparison with carfilzomib + dexamethasone; an added benefit is therefore not proven.

Morbidity

Symptoms

The symptom outcomes were surveyed using the disease-specific instruments European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Core 30 (QLQ-C30) and EORTC Quality of Life Questionnaire – Myeloma (QLQ-MY20). For the benefit assessment, time to 1st deterioration by ≥ 10 points (scale range 0–100) was analysed.

For the symptom outcomes, no statistically significant difference between treatment groups was found. Consequently, there is no hint of added benefit of isatuximab + carfilzomib + dexamethasone in comparison with carfilzomib + dexamethasone for any of them; an added benefit is therefore not proven.

Health status

Health status was measured using the European Quality of Life Questionnaire – 5 Dimensions (EQ-5D VAS). For the outcome of health status, time to 1st deterioration by ≥ 15 points (scale range 0–100) was analysed.

No statistically significant difference between treatment groups was found. Consequently, there is no hint of added benefit of isatuximab + carfilzomib + dexamethasone in comparison with carfilzomib + dexamethasone; an added benefit is therefore not proven.

Health-related quality of life

The health-related quality of life outcomes were surveyed using the disease-specific instruments EORTC QLQ-C30 and EORTC QLQ-MY20. Time to 1st deterioration by ≥ 10 points (scale range 0–100) was analysed.

EORTC QLQ-C30

Physical functioning

For the outcome of physical functioning, no statistically significant difference between treatment arms was found. However, there is an effect modification by R-ISS stage at baseline (I or II versus III) at study inclusion.

For patients in R-ISS stage I or II at baseline, the treatment groups do not statistically significantly differ in the outcome of physical functioning. Consequently, there is no hint of added benefit of isatuximab + carfilzomib + dexamethasone in comparison with carfilzomib + dexamethasone; an added benefit is therefore not proven.

For patients in R-ISS stage III at baseline, there is a statistically significant difference in the outcome of physical functioning in favour of isatuximab + carfilzomib + dexamethasone. For patients in R-ISS stage III, this results in a hint of added benefit.

Global health status, role functioning, emotional functioning, cognitive functioning, social functioning

For these outcomes, no statistically significant difference between treatment groups was found. Consequently, there is no hint of added benefit of isatuximab + carfilzomib + dexamethasone in comparison with carfilzomib + dexamethasone; an added benefit is therefore not proven.

EORTC QLQ-MY20

None of the EORTC QLQ-MY20 outcomes on health-related quality of life (body image, future perspective) showed any statistically significant differences between treatment groups. Consequently, there is no hint of added benefit of isatuximab + carfilzomib + dexamethasone in comparison with carfilzomib + dexamethasone for any of them; an added benefit is therefore not proven.

Side effects

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

For each of the outcomes of SAEs and severe AEs, no statistically significant difference between treatment groups was found. Consequently, there is no hint of greater or lesser harm of isatuximab + carfilzomib + dexamethasone in comparison with carfilzomib + dexamethasone for any of them; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

For the outcome of discontinuation due to AEs, no usable data were available. Consequently, there is no hint of greater or lesser harm of isatuximab + carfilzomib + dexamethasone in comparison with carfilzomib + dexamethasone; greater or lesser harm is therefore not proven.

Specific AEs

Infusion-related reactions

For the outcome of infusion-related reactions (preferred term [PT]), there is a statistically significant difference to the disadvantage of isatuximab + carfilzomib + dexamethasone. Consequently, there is a hint of greater harm of isatuximab + carfilzomib + dexamethasone in comparison with carfilzomib + dexamethasone.

Diseases of the skin and subcutaneous tissue (system organ class [SOC], AEs)

For the outcome of skin and subcutaneous tissue disorders (SOC, AEs), a statistically significant difference was found to the disadvantage of isatuximab + carfilzomib + dexamethasone. Consequently, there is a hint of greater harm of isatuximab + carfilzomib + dexamethasone in comparison with carfilzomib + dexamethasone.

Thrombocytopoenia (PT, severe AEs)

For the outcome of thrombocytopoenia (PT, severe AEs), a statistically significant difference was found in favour of isatuximab + carfilzomib + dexamethasone. Consequently, there is a hint of lesser harm of isatuximab + carfilzomib + 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 presented results, the probability and extent of added benefit of the drug isatuximab in comparison with the ACT have been assessed as follows:

Overall, both favourable and unfavourable effects of different extents, all with the probability of hint, were found for isatuximab + carfilzomib + dexamethasone in comparison with carfilzomib + dexamethasone. They concern both the outcome of health-related quality of life and outcomes on side effects of different degrees of severity.

The favourable effects concern physical functioning in the category of health-related quality of life as well as the outcome of thrombocytopoenia in the serious/severe adverse-events category. For the outcome of physical functioning, this effect is limited to patients in disease stage R-ISS III, for whom there is a hint of major added benefit. For the outcome of thrombocytopoenia, in contrast, a hint of lesser harm with an extent of considerable can be derived.

The unfavourable effects are all specific AEs in the outcome category of non-serious/non-severe AEs. For the outcomes of infusion-related reactions (PT) as well as skin and subcutaneous tissue disorders, there is a hint of greater harm of considerable extent for isatuximab + carfilzomib + dexamethasone versus carfilzomib + dexamethasone.

The effect modification by disease stage at baseline, which was observed in only 1 outcome on health-related quality of life, does not justify a separate benefit to be derived for different patient groups. Furthermore, the distribution of favourable and unfavourable effects is deemed

[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].

balanced, in part because the latter are in the outcome category of non-serious/non-severe AEs. In summary, there is therefore no proof of added benefit of isatuximab + carfilzomib + dexamethasone versus carfilzomib + dexamethasone in patients with multiple myeloma who received at least 1 prior therapy.

Table 3 presents a summary of the probability and extent of added benefit of isatuximab.

Table 3: Isatuximab + carfilzomib + 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[b]	▪ 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**. b. According to the G-BA, it is assumed that high-dose chemotherapy with stem cell transplantation is not an option for the patients at the time of the current therapy. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

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

2.2 Research question

The aim of this report is to assess the added benefit of isatuximab in combination with carfilzomib and dexamethasone (hereinafter isatuximab + carfilzomib + dexamethasone) in comparison with the ACT in adult patients with multiple myeloma who have received at least 1 prior therapy.

The G-BA's specification of the ACT results in the research question presented in Table 4.

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

Indication	ACT[a]
Adult patients with multiple myeloma who have received at least 1 prior therapy[b]	▪ 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. 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**. b. According to the G-BA, it is assumed that high-dose chemotherapy with stem cell transplantation is not an option for the patients at the time of the current therapy. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA's specification of the ACT. To this effect, instead of explicitly selecting a drug combination from the identified options, the company included a study comparing isatuximab in combination with carfilzomib and dexamethasone versus carfilzomib in combination with dexamethasone.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier. RCTs were used for the derivation of 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 cited by the company in the dossier:

- Study list on isatuximab (as of 1 March 2021)
- Bibliographic literature search on isatuximab (most recent search on 1 March 2021)
- Search in trial registries / study results databases on isatuximab (most recent search on 1 March 2021)
- Search on the G-BA website on isatuximab (most recent search on 1 March 2021)

To check the completeness of the study pool:

- Search in trial registries for studies on isatuximab (most recent search on 25 May 2021); see Appendix E of the full dossier assessment for search strategies.

The check did not identify any additional relevant studies.

2.3.1 Included studies

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

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

Study	Study category			Available sources		
	Approval study for the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (yes/no [reference])	Registry entries[b] (yes/no [reference])	Publication and other sources[c] (yes/no [reference])
IKEMA	Yes	Yes	No	Yes [3]	Yes [4,5]	Yes [6-8]

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
G-BA: Federal Joint Committee; RCT: randomized controlled trial

The study pool is consistent with that of the company.

2.3.2 Study characteristics

Table 6 and Table 7 present the study used in the benefit assessment.

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and time period conducted	Primary outcome; secondary outcomes[a]
IKEMA	RCT, open-label, parallel-group	Adults (≥ 18 years of age) with relapsed and/or refractory multiple myeloma[b] and ▪ at least 1 and at most 3 prior therapies[c] and ▪ ECOG-PS ≤ 2	Isatuximab + carfilzomib + dexamethasone (N = 179) Carfilzomib + dexamethasone (N = 123)	Screening: ≤ 21 days Treatment: Until disease progression, unacceptable toxicity, or study discontinuation Follow-up observation[d]: Outcome-specific, at most until death or withdrawal of consent	69 centres in Australia, Brazil, Canada, Czech Republic, France, Greece, Hungary, Italy, Japan, Korea, New Zealand, Russia, Spain, Turkey, United Kingdom, United States Time period: 10/2017 – ongoing Data cut-off: 07/02/2020 (interim analysis)[e]	Primary: PFS Secondary: overall survival, morbidity, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes contain information exclusively on relevant available outcomes from the information provided by the company in Module 4 of the dossier.
b. Measurable disease, defined as M-protein ≥ 0.5 g/dL in serum or M-protein ≥ 200 mg/24 h in urine.
c. Induction therapy followed by stem cell transplantation and consolidation/maintenance therapy is deemed 1 therapy line.
d. Outcome-specific information is provided in Table 8.
e. The data cut-off for the interim analysis was predefined at 65% of 159 PFS events.

AE: adverse event; ECOG-PS: Cooperative Oncology Group Performance Status; M-protein: monoclonal protein; N: number of randomized patients; PFS: progression-free survival; RCT: randomized controlled trial

Table 7: Characterization of the intervention – RCT, direct comparison: isatuximab + carfilzomib + dexamethasone vs. carfilzomib + dexamethasone

(multipage table)

Study	Intervention	Comparison
IKEMA	Isatuximab[a]: ▪ Cycle 1: 10 mg/kg, i.v. on Days 1, 8, 15, and 22 ▪ From Cycle 2: 10 mg/kg, i.v. on Days 1 and 15	–
	Carfilzomib ▪ Cycle 1: 20 mg/m² BSA[b], i.v. on Days 1 and 2, followed by 56 mg/m² BSA[b], i.v. on Days 8, 9, 15, and 16 ▪ From Cycle 2: 56 mg/m² BSA[b], i.v. on Days 1, 2, 8, 9, 15, and 16	Carfilzomib ▪ Cycle 1: 20 mg/m² BSA[b], i.v. on Days 1 and 2, followed by 56 mg/m² BSA[b], i.v. on Days 8, 9, 15, and 16 ▪ From Cycle 2: 56 mg/m² BSA[b], i.v. on Days 1, 2, 8, 9, 15, and 16
	Dexamethasone: ▪ All cycles: 20 mg[c] on Days 1, 2, 8, 9, 15, 16, 22, and 23	Dexamethasone: ▪ All cycles: 20 mg[c] on Days 1, 2, 8, 9, 15, 16, 22, and 23
	Cycle length: 28 days	Cycle length: 28 days
	Dose modifications ▪ Isatuximab: no dose reductions allowed, only treatment interruptions due to toxicity ▪ Carfilzomib and dexamethasone: dose reductions allowed In case of discontinuation of one component, continuation of therapy with the other component(s) was allowed.	
	Premedication before the infusions ▪ For the intervention arm, ▫ 650–1000 mg paracetamol, p.o. 15–30 minutes, but ≤ 60 minutes before isatuximab ▫ Ranitidine 50 mg or equivalent ▫ Diphenhydramine 25–50 mg i.v. or equivalent ▪ For both arms, ▫ Hydration: ≥ 48 hours before the carfilzomib infusions in Cycles 1 and 2 orally (30 mL/kg/day), thereafter upon the treating physician's discretion ▫ Dexamethasone[c, d] 20 mg i.v. (simultaneously part of treatment)	
	Permitted pretreatment ▪ 1–3 antimyeloma therapies **Nonpermitted prior treatment** ▪ α-CD38 therapies if relapse developed during or within 60–days after the end of the CD38 antibody treatment or if not even a minimal response was achieved ▪ Antimyeloma therapies (including dexamethasone) if started ≤ 14 days before randomization ▪ Carfilzomib therapy	

Table 7: Characterization of the intervention – RCT, direct comparison: isatuximab + carfilzomib + dexamethasone vs. carfilzomib + dexamethasone

(multipage table)

Study	Intervention	Comparison
	Permitted concomitant treatment ▪ Antiviral prophylaxis as needed and according to the guidelines of the treating centre ▪ G-CSF in recurrent or serious neutropenia ▪ Palliative radiotherapy ▪ Glucocorticoids, histamines, and analgesics for the treatment of infusion reactions **Nonpermitted concomitant treatment** ▪ Antimyeloma therapies departing from the protocol, including curative radiotherapy ▪ Systemic corticosteroids except as part of protocol-specified therapy or treatment of hypersensitivity reactions	
a. Isatuximab is administered immediately before carfilzomib. b. In patients with a BSA > 2.2 m², the dose is calculated using a BSA of 2.2 m². c. Intravenously on the days of isatuximab- and/or carfilzomib administration, orally on the other days; intravenous administration 15–30 minutes (but not > 60 minutes) before isatuximab administration in the intervention arm. In the control arm and on the days without isatuximab in the intervention arm, it is given ≥ 30 minutes before carfilzomib administration. d. If dexamethasone is discontinued early while the other study drugs are continued, premedication with methyl prednisolone 100 mg i.v. can be administered upon the treating physician's discretion. α-CD38: CD38 antibody; BSA: body surface area; CD38: cluster of differentiation 38; G-CSF: granulocyte colony-stimulating factor; i.v.: intravenous; p.o.: orally; RCT: randomized controlled trial		

IKEMA is an ongoing, open-label, randomized, multicentric study comparing isatuximab + carfilzomib + dexamethasone versus carfilzomib + dexamethasone.

The study included adult patients with relapsed and/or refractory multiple myeloma who have already received 1 to 3 prior therapies. Additionally, they had to exhibit measurable disease in the form of an elevated monoclonal protein (M-protein) concentration (≥ 0.5 g/dL in serum or ≥ 200 mg/24 h in urine). Prior treatment with a cluster of differentiation 38 (CD38) antibody was allowed if no relapse occurred during treatment or within 60 days after the end of treatment with the anti-CD38 antibody and at least minimal response was achieved. The study excluded patients with primary refractory myeloma, prior carfilzomib therapy as well as patients whose general condition corresponded to an Eastern Cooperative Oncology Group – Performance Status (ECOG-PS) > 2; hence, no data were available on these patients.

A total of 302 patients were randomly allocated in a 3:2 ratio to treatment with isatuximab + carfilzomib + dexamethasone (N = 179) or treatment with carfilzomib + dexamethasone (N = 123). Randomization applied the stratification factors of disease stage in accordance with the R-ISS (I or II versus III versus not classified) as well as number of prior treatment lines (1 versus > 1).

Treatment with isatuximab + carfilzomib + dexamethasone or carfilzomib + dexamethasone was administered according to the regimen shown in Table 7, and in both study arms; it

corresponded largely to the specifications of the Summary of Product Characteristics (SPC) [9,10]. However, the patients in the intervention arm received 50 mg ranitidine (or a comparable H_2 antagonist) as premedication for the isatuximab infusions. First, ranitidine premedication is not mentioned in the isatuximab SPC, and second, the approval for ranitidine-containing drugs is currently suspended in Germany [11]. However, this situation does not result in the exclusion of the IKEMA study from the present benefit assessment.

The available documents do not show any restrictions regarding possible follow-up therapies or whether a switch between arms is permitted.

Primary outcome of the IKEMA study was PFS. As patient-relevant secondary outcomes, overall survival as well as morbidity, health-related quality of life, and adverse events (AEs) outcomes were surveyed.

Data cut-off dates

The company's dossier presents results on the interim data cut-off of 7 February 2020 for all outcomes. This cut-off was predefined and applied after 65% of 159 PFS events had occurred.

In Module 4 B, the company points out that, for the outcome of overall survival, the 7 February 2020 interim analysis was not planned a priori but was to be conducted 3 years after the primary PFS analysis. In the company's view, the available data cut-off does not allow a final assessment of the outcome of overall survival, because a corresponding analysis is to be undertaken 3 years after the primary PFS analysis.

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 follow-up observation – RCT, direct comparison: isatuximab + carfilzomib + dexamethasone vs. carfilzomib + dexamethasone

Study **Outcome category** **Outcome**	**Planned follow-up observation**
IKEMA	
Mortality	
Overall survival	Until death or withdrawal of consent
Morbidity[a]	
Symptoms (EORTC QLQ-C30, EORTC QLQ MY20)	Up to 90 ± 5 days after the last dose of the study drug
Health status (EQ-5D VAS)	Up to 90 ± 5 days after the last dose of the study drug
Health-related quality of life[a]	
EORTC QLQ-C30, EORTC QLQ-MY20	Up to 90 ± 5 days after the last dose of the study drug
Side effects	
All outcomes of the AE category	Up to 30 days after the last dose of the study drug

a. Module 4 provided discrepant information. The information presented here is from the other study documents.

EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life Questionnaire – 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

The durations of follow-up observation for the outcomes of morbidity, health-related quality of life, and side effects are systematically shortened since they were surveyed only for the period of treatment with the study drug (plus 30 days for side effects or 90 days for patient-reported outcomes). To be able to draw a reliable conclusion for the entire study period or until patient death, these outcomes, like survival, would have to be surveyed and analysed over the entire period.

Characterization of the study population

Table 9 shows the patient characteristics of the included study.

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

Study Characteristic Category	**Isatuximab + carfilzomib + dexamethasone N = 179**	**Carfilzomib + dexamethasone N = 123**
IKEMA		
Age [years], mean (SD)	63 (10)	63 (10)
Sex [f/m], %	44/56	45/55
Ancestry, n (%)		
White	131 (73)	83 (68)
African American	5 (3)	4 (3)
Asian	26 (15)	24 (20)
Mixed ancestry	3 (2)	0 (0)
Unknown	14 (8)	12 (10)
Geographic region, n (%)		
Europe	85 (48)	60 (49)
America	24 (13)	20 (16)
Asia	25 (14)	21 (17)
Other countries	45 (25)	22 (18)
Time between initial diagnosis and randomization [years], median (SD)	4.1 (3.0)	4.3 (3.2)
R-ISS stage at baseline, n (%)		
I	45 (25)	33 (27)
II	110 (62)	70 (57)
III	16 (9)	8 (7)
Unknown	8 (5)	12 (10)
MM subtype at baseline, n (%)		
IgG	126 (70)	85 (69)
IgA	38 (21)	30 (24)
IgM	0 (0)	0 (0)
IgD	4 (2)	1 (1)
IgE	0 (0)	0 (0)
Kappa light chains (urine)	5 (3)	4 (3)
Lambda light chains (urine)	6 (3)	3 (2)
Patients with bone lesions (after IRC) at baseline, n (%)[a]		
Yes	126 (70)	92 (75)
No	41 (23)	27 (22)
Cytogenetic risk (defined for R-ISS), n (%)		
High risk	42 (24)	31 (25)
Normal risk	114 (64)	78 (63)
Unknown or missing	23 (13)	14 (11)
Number of prior antimyeloma therapy lines[b], n (%)		

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

Study Characteristic Category	**Isatuximab + carfilzomib + dexamethasone N = 179**	**Carfilzomib + dexamethasone N = 123**
1	79 (44)	55 (45)
2	64 (36)	36 (29)
3	33 (18)	30 (24)
> 3	3 (2)	2 (2)
Patients with at least 1 transplantation, n (%)	119 (67[c])	69 (56)
Allogeneic stem cell transplantation	3 (2)	0 (0)
Autologous stem cell transplantation	116 (65)	69 (56)
Number and type of relevant prior treatments, n (%)		
Alkylating agents	169 (94)	101 (82)
Anthracyclines	23 (13)	14 (11)
PI	166 (93)	105 (85)
IMiD	136 (76)	100 (81)
HDAC inhibitors	1 (1)	2 (2)
Corticosteroids	179 (100)	123 (100)
Vinca alkaloids	14 (8)	9 (7)
Monoclonal antibodies	5 (3)	1 (1)
Other	23 (13)	22 (18)
Refractory status at baseline, n (%)		
Relapsed and refractory	122 (68)	94 (76)
Primary refractory	0 (0)	0 (0)
Relapsed	57 (32)	29 (24)
Refractory to IMiD, n (%)	78 (44)	58 (47)
To lenalidomide	57 (32)	42 (34)
To pomalidomide	4 (2)	4 (3)
Refractory to PI, n (%)	56 (31)	44 (36)
To bortezomib	52 (29)	39 (32)
To ixazomib	5 (3)	8 (7)
Refractory to IMiD and PI, n (%)	35 (20)	27 (22)
To lenalidomide and bortezomib	26 (15)	19 (15)
To lenalidomide and ixazomib	3 (2)	6 (5)
To lenalidomide, bortezomib, and ixazomib	1 (1)	3 (2)
Refractory to the most recent treatment, n (%)	89 (50)	73 (59)
To lenalidomide	36 (20)	31 (25)
To bortezomib	32 (18)	23 (19)
To pomalidomide	4 (2)	4 (3)
To lenalidomide and bortezomib	5 (3)	4 (3)

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

Study Characteristic Category	Isatuximab + carfilzomib + dexamethasone N = 179	Carfilzomib + dexamethasone N = 123
Treatment discontinuation[d], n (%)	84 (46.9)	84 (68.3)
Study discontinuation, n (%)	ND	ND

a. The analysis according to the IRC included 167 patients in the intervention arm and 119 patients in the control arm. The percentages are based on the ITT population.
b. Induction therapy followed by stem cell transplantation and consolidation/maintenance therapy is deemed 1 therapy line.
c. IQWiG calculations.
d. Discontinuation of all drug components. In both arms, the most common reason for treatment discontinuation was disease progression: 52 (29%) versus 49 (40%), followed by AEs: 15 (8%) versus 17 (14%) and withdrawal of patient consent: 11 (6%) versus 14 (11%).

AE: adverse event; f: female; HDAC: histone deacetylase; Ig: immunoglobulin; IMiD: immunomodulatory drug; IRC: independent review committee; ITT: intention to treat; m: male; MM: multiple myeloma; n: number of patients in the category; N: number of randomized patients; ND: no data; PI: proteasome inhibitor; RCT: randomized controlled trial; R-ISS: Revised International Staging System; SD: standard deviation

The IKEMA study arms exhibited, for the most part, comparable patient characteristics. On average, patients were 63 years of age, and about 70% were white. In both arms, about 55% of the population was male. All patients had relapsed myeloma, and 72% had relapsed and refractory myeloma. At about 85%, the majority of patients was in R-ISS stage I or II at the time of randomization. In contrast, only 8% were in R-ISS stage III. About 45% of patients had received 1 prior antimyeloma therapy, with the percentage of patients with 2 therapy lines being slightly higher in the intervention arm (36% versus 29%) and that of patients with 3 prior therapy lines being slightly lower (18% versus 24%). The percentage of patients with autologous stem cell transplantation was slightly higher in the intervention arm (65%) than in the control arm (56%). The most commonly used drugs in prior therapies were proteasome inhibitors (about 90%) and immunomodulatory agents (about 78%). In contrast, few patients (about 2%) had received monoclonal antibodies as prior therapy. About 45% of patients were refractory to an immunomodulatory drug and 33% to a proteasome inhibitor. About 21% of patients were refractory to both a proteasome inhibitor and an immunomodulatory drug (i.e. double refractory). In the intervention arm, 50% of patients were refractory to their most recent treatment, compared to a slightly higher figure, 59%, in the control arm.

Data on the course of the study

Table 10 shows the median duration of patient treatment as well as the median duration of follow-up observation for individual outcomes.

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

Study **Duration of the study phase** **Outcome category**	**Isatuximab + carfilzomib + dexamethasone** **N = 179**	**Carfilzomib + dexamethasone** **N = 123**
IKEMA		
Treatment duration [weeks][a]		
Median [Q1; Q3]	80.0 [40.0; 89.0]	61.4 [28.9; 84.0]
Mean (SD)	ND	ND
Follow-up duration [months]		
Overall survival		
Median [Q1; Q3]	20.7 [19.4; 22.1][b]	
Mean (SD)	ND	ND
Morbidity		
Symptoms (EORTC QLQ-C30)	ND	ND
Symptoms (EORTC QLQ-MY20)	ND	ND
Health status (EQ-5D VAS)	ND	ND
Health-related quality of life (EORTC QLQ C30 and EORTC QLQ-MY20)	ND	ND
Side effects	ND	ND

a. Module 4 B did not provide any information on the respective treatment durations with the different components of the study drugs.
b. Data were not presented separately for each study arm.
EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; max: maximum; min: minimum; N: number of analysed patients; ND no data; Q1: 1st quartile; Q3: 3rd quartile; QLQ-C30: Quality of Life Questionnaire Core 30; QLQ-MY20: Quality of Life Questionnaire Multiple Myeloma 20; RCT: randomized controlled trial; SD: standard deviation

The median treatment duration in the intervention arm of the IKEMA study was about a third longer than in the control arm (80.0 versus 61.4 months). Differences between treatment arms are largely in treatment discontinuation rates, mainly due to disease progression. Data on follow-up durations for both study arms combined are available only for the outcome of overall survival (median of 20.7 months). For the two study arms separately, no data are available for this outcome or for the further patient-relevant outcomes. Since the follow-up observation for the further outcomes was coupled to treatment duration (see Table 8), the between-arm difference in observation duration is presumably equivalent to the difference in treatment duration. See Section 2.4.2 regarding the effects on the risk of bias on the outcome level.

Information on subsequent therapies

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

Table 11: Information on subsequent antineoplastic therapies[a] – RCT, direct comparison: isatuximab + carfilzomib + dexamethasone vs. carfilzomib + dexamethasone (IKEMA study)

Study Drug class Drug	Patients with subsequent therapy n (%)	
	Intervention N = 179	Comparison N = 123
IKEMA		
Total	47 (26.3)	53 (43.1)
IMiD	39 (21.8)[b]	42 (34.1)[b]
Corticosteroids	38 (21.2)[b]	44 (35.8)[b]
Monoclonal antibodies	11 (6.1)[b]	29 (23.6)[b]
Daratumumab	10 (5.6[b])	25 (20.3[b])

a. Listed are the most common subsequent therapies.
b. IQWiG calculations.

IMiD: immunomodulatory drug; n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial

After discontinuation of the study drug, patients were allowed to receive antimyeloma therapies. The percentage of patients with at least 1 subsequent therapy was lower in the intervention arm than in the comparator arm (26.3% versus 43.1%) [6,8]. In the intervention arm, about 21% of patients received immunomodulatory drugs, and the same percentage received corticosteroids. For each of these drug classes, the percentage was higher, at 35%, in the control arm. An additional, more pronounced between-arm difference was found, as expected, regarding subsequent therapies with monoclonal antibodies: This drug class was used to treat 6.1% of patients in the intervention arm, but 23.6% in the control arm, with α-CD38-therapy with daratumumab was the most commonly used antibody therapy in both arms. No data are available on proteasome inhibitor-based subsequent therapies.

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: isatuximab + carfilzomib + dexamethasone vs. carfilzomib + dexamethasone

Study	Adequate random sequence generation	Allocation concealment	Blinding		Results-independent reporting	No additional aspects	Risk of bias at study level
			Patients	Treatment providers			
IKEMA	Yes	Yes	No	No	Yes	Yes	Low

RCT: randomized controlled trial

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

Restrictions resulting from the open-label study design are described in Section 2.4.2 under risk of bias at outcome level.

Transferability of the study results to the German healthcare context

The company stated that the study was conducted predominantly in countries belonging to the Western world in terms of their social systems, culture, and ethnology. At 48%, nearly half of randomized patients reportedly come from Europe, and more than two thirds (70.9%) are reportedly white. The slight majority (56.0%) of male patients was in line with real data from everyday practice showing that male patients were more commonly affected by the disease [12,13]. In the company's view, it can therefore be assumed that the study population reflects the healthcare context in Germany.

The company did not present any further information on the transferability of study results to the German healthcare context.

2.4 Results on added benefit

2.4.1 Outcomes included

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

- Mortality
  - Overall survival
- Morbidity
  - Symptoms measured with the symptom scales of the European Organization and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) Core30 (C30)
  - Symptoms, measured with the symptom scales of the EORTC QLQ Multiple Myeloma 20 (MY20)
  - Health status as measured by the European Quality of Life Questionnaire – 5 Dimensions (EQ-5D) visual analogue scale (VAS)
- Health-related quality of life
  - EORTC QLQ-C30, scales on health-related quality of life
  - EORTC QLQ-MY20, scales on health-related quality of life
- Side effects
  - SAEs
  - Severe AEs (Common-Terminology-Criteria-for-Adverse-Events [CTCAE] grade ≥ 3)
  - Discontinuation due to AEs

- Infusion reactions
- Further specific AEs

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

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

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

Study	Outcomes								
	overall survival	Symptoms (EORTC QLQ-C30 and EORTC QLQ-MY20)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-MY20)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Infusion-related reactions[b]	Other specific AEs[a, c]
IKEMA	Yes	Yes	Yes	Yes	Yes	Yes	No[d]	Yes	Yes

a. Severe AEs are operationalized as CTCAE ≥ 3.
b. Operationalized as PT "infusion-related reaction."
c. The following events were assessed (MedDRA coding): diseases of the skin and subcutaneous tissue (SOC, AEs), thrombocytopoenia (PT, severe AEs).
d. No usable analyses available; see further reasoning in the text.

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; PT: preferred term; QLQ-C30: Quality of Life Questionnaire Core 30; QLQ-MY20: Quality of Life Questionnaire Multiple Myeloma 20; RCT: randomized controlled trial; SAE: serious adverse event; SOC: system organ class; VAS: visual analogue scale

Comment on the included outcomes and analyses

Symptoms and health-related quality of life

- For the EORTC QLQ-C30 and EORTC-MY20, the company's dossier presented responder analyses for time until a change by ≥ 10 and by ≥ 15 points of the scale range (scale ranges of 0–100). As discussed in the IQWiG General Methods [1,14], 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. For EORTC QLQ-C30 and its supplementary modules, the analysis with the previously accepted response threshold of 10 points was viewed as a sufficient approximation to an analysis with a 15% threshold (15 points) and was used for the benefit assessment (for an explanation, see [15]). Irrespective of the above, for a transition period until the revised module templates for the dossier enter into force, primarily analyses with the previously accepted response threshold of 10 points were used for the EORTC QLQ-C30 and all additional EORTC modules (see FAQs from the G-BA: [16]).

- For the outcome of health status (EQ-5D VAS), the company's dossier presents responder analyses for time to a change by ≥ 7 points or ≥ 10 points, respectively (scale range 0 – 100). These were not used for the dossier assessment but presented as supplementary information in Appendix D of the full dossier assessment. Further, Appendix 4 G of the company's dossier provides responder analyses with the response criterion of 15% of the scale range. They were used to derive added benefit, but the company's Module 4 B did not submit any subgroup analyses on them.

- For the outcomes from EORTC QLQ-C30, EORTC QLQ-MY20, and EQ-5D VAS, the company presented responder analyses with the following operationalizations:
  - Time to 1st deterioration/improvement
  - Time to definitive deterioration/improvement:

  From these operationalizations, time to 1st deterioration was used. Due to the progressive course of disease to be expected in the present therapeutic indication, an analysis of deterioration of health status is primarily relevant for the present benefit assessment.

  The analyses of time to 1st deterioration were preferred over the analyses of time to definitive deterioration because no information was available on the operationalization of time to definitive deterioration or on the description of the analyses. Hence it remains unclear, for instance, whether a deterioration is considered definitive if the response criterion is also met in all subsequent observations and how patients were handled who had a (single) deterioration at the last recording time.

Side effect outcomes

- For the outcome of discontinuation due to AEs, the company presented only analyses of time until discontinuation of all drug components due to AEs. In view of the present data situation with 3 drugs in the intervention arm and 2 drugs in the comparator arm, an analysis of only the discontinuation of all drug components cannot be meaningfully interpreted. Analyses of discontinuation of at least 1 drug component would be a preferable outcome since every AE which leads to discontinuation of any treatment component is relevant. However, Module 4 B does not provide such analyses. The available data on the outcome of discontinuation due to AEs are unusable overall.

- In Module 4 B, the company conceded that the recorded AEs did not include any progression-associated AEs; this was not stated in the study protocol, however. Likewise, the company failed to specify these AEs or the PTs it viewed as progression. Appendix 4 B of the company's dossier presents supplementary analyses without the MedDRA (Medical Dictionary for Regulatory Activities) System Organ Class (SOC) "Benign, malignant, and unspecified neoplasms (including cysts and polyps)". These analyses were disregarded because, rather than representing progression of the underlying disease, the events in this SOC largely represent secondary primary tumours (e.g. skin cancer) [8]; hence, excluding these events is inappropriate. For total rates of AEs, the employed data therefore included progression-related AEs as defined by the company in Module 4 B since any disease-related events potentially included in this analysis would presumably not affect the conclusion in a relevant way. Nevertheless, an (additional) analysis of AEs excluding any disease-related events, as per the dossier template, would have been appropriate.
- In line with the study protocol, for the outcomes pertaining to side effects, laboratory values were reported as AEs only if they led to treatment discontinuation or dose modification or constituted an SAE. This resulted in potentially incomplete recording, particularly of severe AEs. For instance, the percentage of patients with neutropenia is much higher when it is calculated based on laboratory values than based on the AE recording: Neutropenia was identified from laboratory results in 55% of patients of the intervention arm and 43% of patients in the control arm, while it was reported as an AE in only 4.5% of those in the intervention arm and 0.8% of those in the control arm. Severe neutropenia (CTCAE grade 3 or 4) in the form of an abnormal laboratory result was reported for 19% of patients in the intervention arm and 7% of those in the control arm but recorded as a side effect in only 4% and 0%, respectively. The available documents fail to show the extent to which the total rates of severe AEs are affected by these missing events. Overall, the analyses on side effects are deemed usable for the present assessment, but the informative value of results on severe side effects is limited, which was taken into account in the assessment of certainty of results (see Section 2.4.2).
- The IKEMA study protocol stated that infusion reactions were defined as AEs typically occurring within 24 hours after the infusion and deemed by the investigator to be related to the drug administration. The study documents show that, wherever possible, a clinical diagnosis of an infusion-related reaction was to be reported (e.g. through the PTs "infusion-related reaction" or "hypersensitivity") rather than the individual symptoms present. However, in addition to a clinical diagnosis, the underlying symptoms were to be recorded in a separate documentation form (case report form, CRF). It must be noted that the infusion-related events recorded in the separate CRF, i.e. the symptoms, were not included in the general analysis of all AEs (treatment emergent AEs [TEAEs]) and are therefore not found in the tables of common AEs (see Table 23 through Table 25 of the full dossier assessment).

In the present situation where both study arms receive i.v. administration, using the analyses on the PT "infusion-related reaction" for the assessment is deemed adequate. The symptoms on which the analysis is based are presented in Table 26 of the full dossier assessment. The interpretability of results is limited because no specific criteria (e.g. a predefined list with PTs) were specified to guide investigators as to whether an AE was to be classified as infusion-related. Overall, the analyses on this outcome are deemed usable for the present assessment, but the informative value of the results on infusion-related reactions is limited; this was taken into account in the assessment of certainty of results (see Section 2.4.2).

Further, it should be noted that the analysis of infusion-related reactions complicated the interpretation of the results on common PTs/SOCs (also see [1]), specifically for the PTs/SOCs that were commonly infusion related (Table 26 of the full dossier assessment). For instance, the analysis of infusion-related reactions allows drawing conclusions only on AEs physicians linked to the infusion. Although it would be necessary, no additional analysis was done of all symptomatic AEs which occurred over the course of the study (TEAEs including infusion-related events) as part of TEAEs. Consequently, an analysis of all events which occurred in the course of the study on the PT and SOC levels might possibly change the effect estimate for the individual PTs. This is illustrated by the PT fever, which is documented as an infusion-related AE in 7 (4.0%) patients versus 1 (0.8%) patient and as a non-infusion-related event in 16 (9.0%) versus 18 (14.8%) patients (compare Table 23 and Table 26 of the full dossier assessment). Adding the two percentages is not an option, because a patient might have experienced both an infusion-related event and a non-infusion-related event. Hence, data recording is incomplete for individual PTs which often occurred as infusion-related events (e.g. dyspnoea and cough, see Table 26 of the full dossier assessment). This makes it impossible to draw definitive conclusions on potential effects on the PT/SOC level for the respective SOCs/PTs. This does not affect the specific AEs included in the present assessment (thrombocytopoenia [PT] and diseases of the skin and subcutaneous tissue [SOC, AEs]) because according to the information provided in the study documents, they are not deemed infusion-related AEs.

2.4.2 Risk of bias

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

Table 14: Risk of bias at study and outcome levels – RCT, direct comparison: isatuximab + carfilzomib + dexamethasone vs. carfilzomib + dexamethasone

Study	Study level	Outcomes										
		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[b]	Other specific AEs[c]
IKEMA	L	L	H[d, e]	H[d, e]	H[d,e]	H[d,e]	H[d, e]	L	L	–[f]	H[d, e]	H[d, e]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. Operationalized as PT "infusion-related reaction."
c. The following events were assessed (MedDRA coding): diseases of the skin and subcutaneous tissue (SOC, AEs), thrombocytopoenia (PT, severe AEs).
d. Lack of blinding with subjective outcome recording (in case of AEs, this aspect affects only non-serious/ non-severe AEs).
e. Differing survey return rates or differing treatment durations and resulting observation durations between treatment arms. This might be due to potentially informative reasons.
f. No usable data available; see Section 2.4.1 of the present dossier assessment for the reasoning.

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; PT: preferred term; QLQ-C30: Quality of Life Questionnaire Core 30; QLQ-MY20: Quality of Life Questionnaire Multiple Myeloma 20; RCT: randomized controlled trial; SAE: serious adverse event; SOC: system organ class; VAS: visual analogue scale

The risk of bias for the outcomes of overall survival, SAEs, and severe AEs were rated as low. Despite different treatment durations and resulting differences in observation durations, there is a low risk of bias for the outcomes SAEs and severe AEs. Since the observed censoring percentages are low, the influence of potentially informative censoring is deemed irrelevant (see Appendix A of the full dossier assessment). This concurs with the company's assessment.

In contrast, the risk of bias is deemed high for the results of patient-reported outcomes on symptoms (symptom scales of the EORTC QLQ-C30 and the EORTC QLQ-MY20), health-related quality of life (functioning scales of the EORTC QLQ-C30 and the EORTC QLQ-MY20) as well as health status (EQ-5D VAS). This is due to the lack of blinding with subjective outcome recording as well as differences in survey return rates. The company concurred in deeming the risk of bias of these outcomes as high, but it justified this only with the lack of blinding with subjective outcome recording by patients.

For the results of the specific AEs, the risk of bias is deemed high because of between-group differences in follow-up observation durations for potentially informative reasons. For specific

AEs, in the outcome category of non-serious/non-severe AEs, lack of blinding with subjective outcome recording further contributes to the high risk of bias. This concurs with the company's assessment. The company's reasoning, however, is based on the total rate of any AEs aggregating both patient-relevant outcomes and non-patient-relevant outcomes.

However, the certainty of results is further reduced for severe AEs and infusion-related reactions (operationalized as the PT "infusion-related reactions") (see Section 2.4.1).

2.4.3 Results

Table 15 summarizes the results on the comparison of isatuximab + carfilzomib + dexamethasone versus carfilzomib + dexamethasone in patients with multiple myeloma who received at least 1 prior therapy. Where necessary, calculations conducted by IQWiG are provided in addition to the data from the company's dossier.

Kaplan-Meier curves on the event-time analyses are found in Appendix A of the full dossier assessment, and results on common AEs are presented in Appendix B of the full dossier assessment.

Table 15: Results (mortality, morbidity, health-related quality of life, AEs) – RCT, direct comparison: isatuximab + carfilzomib + dexamethasone vs. carfilzomib + dexamethasone (multipage table)

Study Outcome category Outcome	Isatuximab + carfilzomib + dexamethasone		Carfilzomib + dexamethasone		Isatuximab + carfilzomib + 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]
IKEMA					
Mortality					
Overall survival	179	NR 31 (17.3)	123	NR 25 (20.3)	0.88 [0.52; 1.50]; 0.644
Morbidity					
Symptoms (EORTC QLQ-C30)[b]					
Fatigue	179	3.8 [2.8; 4.7] 126 (70.4)	123	4.8 [2.8; 7.5] 81 (65.9)	1.22 [0.92; 1.62]; 0.167
Nausea and vomiting	179	18.6 [12.0; NC] 89 (49.7)	123	NR [10.5; NC] 50 (40.7)	1.20 [0.85; 1.70]; 0.310
Pain	179	7.6 [3.8; 12.2] 106 (59.2)	123	16.2 [4.9; 21.3] 66 (53.7)	1.26 [0.92; 1.72]; 0.144
Dyspnoea	179	5.2 [3.7; 8.4] 116 (64.8)	123	5.8 [3.9; 12.9] 71 (57.7)	1.16 [0.86; 1.56]; 0.338
Insomnia	179	7.4 [4.7; 12.4] 106 (59.2)	123	8.4 [5.7; 15.2] 71 (57.7)	1.09 [0.80; 1.48]; 0.583
Appetite loss	179	14.3 [10.2; NC] 92 (51.4)	123	21.3 [12.3; NC] 55 (44.7)	1.18 [0.85; 1.66]; 0.322
Constipation	179	NR [14.2; NC] 76 (42.5)	123	NR [17.0; NC] 48 (39.0)	1.12 [0.78; 1.61]; 0.536
Diarrhoea	179	11.1 [6.5; 17.3] 99 (55.3)	123	NR [9.5; NC] 54 (43.9)	1.33 [0.95; 1.86]; 0.090
Symptoms (EORTC QLQ-MY20)[b]					
Symptoms of disease	179	12.7 [6.6; 19.7] 97 (54.2)	123	21.6 [9.3; NC] 58 (47.2)	1.22 [0.88; 1.69]; 0.240
Side effects	179	7.4 [5.6; 11.6] 109 (60.9)	123	13.5 [6.5; NC] 63 (51.2)	1.18 [0.87; 1.62]; 0.290
Health status (EQ-5D VAS)[c]	179	NR [13.2; NC] 79 (44.1)	123	16.8 [7.5; NC] 58 (47.2)	0.88 [0.62; 1.23]; 0.450

Table 15: Results (mortality, morbidity, health-related quality of life, AEs) – RCT, direct comparison: isatuximab + carfilzomib + dexamethasone vs. carfilzomib + dexamethasone (multipage table)

Study Outcome category Outcome	Isatuximab + carfilzomib + dexamethasone		Carfilzomib + dexamethasone		Isatuximab + carfilzomib + 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]
Health-related quality of life					
EORTC QLQ-C30[d]					
Global health status	179	5.9 [3.8; 10.9] 115 (64.2)	123	5.8 [3.8; 13.5] 71 (57.7)	1.19 [0.88; 1.61]; 0.255
Physical functioning	179	10.4 [6.5; 16.7] 102 (57.0)	123	11.2 [6.4; NC] 65 (52.8)	1.10 [0.80; 1.52]; 0.539
Role functioning	179	5.8 [3.8; 10.2] 111 (62.0)	123	5.8 [3.9; 21.5] 69 (56.1)	1.19 [0.88; 1.61]; 0.261
Emotional functioning	179	12.9 [7.7; NC] 92 (51.4)	123	16.9 [6.6; NC] 60 (48.8)	1.06 [0.76; 1.47]; 0.734
Cognitive functioning	179	7.8 [4.8; 11.3] 112 (62.6)	123	7.5 [5.1; 12.0] 74 (60.2)	1.09 [0.81; 1.48]; 0.554
Social functioning	179	4.7 [3.1; 6.5] 118 (65.9)	123	4.7 [2.9; 8.6] 76 (61.8)	1.08 [0.81; 1.45]; 0.588
EORTC QLQ-MY20[b]					
Body image	179	9.0 [6.5; 15.7] 102 (57.0)	123	20.6 [7.3; NC] 59 (48.0)	1.22 [0.88; 1.70]; 0.225
Future perspective	179	10.6 [5.9; NC] 94 (52.5)	123	8.4 [5.0; 19.6] 69 (56.1)	0.90 [0.66; 1.24]; 0.530
Side effects					
AEs (supplementary information)[e]	177	0.2 [0.1; 0.2] 172 (97.2)	122	0.4 [0.3; 0.6] 117 (95.9)	–
SAEs[e]	177	12.6 [9.3; 17.3] 105 (59.3)	122	13.8 [9.2; 21.8] 70 (57.4)	1.08 [0.80; 1.47]; 0.616
Severe AEs[e, f]	177	5.6 [4.5; 7.8] 136 (76.8)	122	6.6 [4.6; 10.5] 82 (67.2)	1.22 [0.93; 1.62]; 0.154
Discontinuation due to AEs	No usable data[g]				
Infusion-related reactions (PT, AEs)[h]	177	NR 79 (44.6)	122	NR 4 (3.3)	17.61 [6.43; 48.19]; < 0.001

Table 15: Results (mortality, morbidity, health-related quality of life, AEs) – RCT, direct comparison: isatuximab + carfilzomib + dexamethasone vs. carfilzomib + dexamethasone (multipage table)

Study Outcome category Outcome	Isatuximab + carfilzomib + dexamethasone		Carfilzomib + dexamethasone		Isatuximab + carfilzomib + 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]
Diseases of the skin and subcutaneous tissue (SOC, AEs)	177	NR 49 (27.7)	122	NR 16 (13.1)	2.23 [1.26; 3.93]; 0.005
Thrombocytopoenia (PT, severe AEs[f])	177	NR 4 (2.3)	122	NR 10 (8.2)	0.26 [0.08; 0.83]; 0.015

a. HR and CI are based on a stratified proportional hazards model; p-value is based on a stratified log-rank test. Stratification factors are the number of prior therapy lines (1 vs. >1) as well as the R-ISS stage (I or II vs. III vs. not classified).
b. Time to 1st deterioration, defined as a score increase by at least 10 points from baseline.
c. Time to 1st deterioration, defined as a score decrease by at least 15 points from baseline.
d. Time to 1st deterioration, defined as a score decrease by at least 10 points from baseline.
e. Total rate including AEs ascribed to progression of the underlying disease.
f. Operationalized as CTCAE grade ≥ 3.
g. No usable data available; see Section 2.4.1 of the present dossier assessment for the reasoning.
h. Operationalized as PT "infusion-related reaction."

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; NR: not reached; PT: preferred term; QLQ-C30: Quality of Life Questionnaire Core 30; QLQ-MY20: Quality of Life Questionnaire Multiple Myeloma 20; R-ISS: Revised International Staging System; RCT: randomized controlled trial; SAE: serious adverse event; SOC: system organ class; VAS: visual analogue scale

The available data allow deriving no more than indications, e.g. of an added benefit, for the outcomes of overall survival and SAEs. At most hints, e.g. of added benefit, can be derived for severe AEs due to the limited certainty of results (see Sections 2.4.1 and 2.4.2); the same is true for all other outcomes due to the high risk of bias.

Mortality

Overall survival

For the outcome of overall survival, the IKEMA study fails to show a statistically significant difference between treatment groups. Consequently, there is no hint of added benefit of isatuximab + carfilzomib + dexamethasone in comparison with carfilzomib + dexamethasone; an added benefit is therefore not proven.

This departs from the company's assessment, which derived an indication of nonquantifiable added benefit because it claimed a positive trend of the effect for the outcome of overall survival.

Morbidity

Symptoms (EORTC QLQ-C30)

The symptoms outcomes were surveyed using the disease-specific instruments EORTC QLQ-C30 and EORTC QLQ-MY20. The analyses on time to 1st deterioration by ≥ 10 points were used in the individual symptom scales. None of the symptom scales of the EORTC QLQ-C30 (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, and diarrhoea) showed any statistically significant differences between treatment groups. For the EORTC QLQ-MY20 as well, none of the symptom scales (disease symptoms, side effects) showed any statistically significant differences between treatment groups. Consequently, there is no hint of added benefit of isatuximab + carfilzomib + dexamethasone in comparison with carfilzomib + dexamethasone for any of them; an added benefit is therefore not proven.

This departs from the company's assessment, which claimed a hint of considerable added benefit for the outcome of nausea and vomiting on the basis of the analysis of time until definitive improvement by ≥ 10 points. For the EORTC QLQ-MY20 symptoms scales, no statistically significant difference between treatment groups was found by the company either.

Health status (EQ-5D VAS)

For the outcome of health status (as measured using EQ-5D VAS), the analysis of time to 1st deterioration by ≥ 15 points) was used. No statistically significant difference between treatment groups was found. Consequently, there is no hint of added benefit of isatuximab + carfilzomib + dexamethasone in comparison with carfilzomib + dexamethasone; an added benefit is therefore not proven.

This concurs with the company's approach in that, for health status measured using EQ-5D VAS, the company also does not see any statistically significant difference between treatment groups. However, the company drew no explicit conclusion regarding added benefit.

Health-related quality of life

EORTC QLQ-C30

For the outcome of health-related quality of life, measured using EORTC QLQ-C30, the present benefit assessment uses time to 1st deterioration by ≥ 10 points on the individual functioning scales.

Physical functioning

For the outcome of physical functioning, there is an effect modification by the characteristic of R-ISS at baseline.

For patients in R-ISS stage I or II, there is no statistically significant difference between treatment groups. Consequently, there is no hint of added benefit of isatuximab + carfilzomib + dexamethasone in comparison with carfilzomib + dexamethasone; an added benefit is therefore not proven.

For patients in R-ISS stage III, there is a hint of added benefit of isatuximab + carfilzomib + dexamethasone in comparison with carfilzomib + dexamethasone.

This deviates from the approach used by the company, which derived no added benefit of isatuximab + carfilzomib + dexamethasone for this outcome.

Global health status, role functioning, emotional functioning, cognitive functioning, social functioning

For these outcomes, no statistically significant differences between treatment groups were found. Consequently, there is no hint of added benefit of isatuximab + carfilzomib + dexamethasone in comparison with carfilzomib + dexamethasone; an added benefit is therefore not proven.

This departs from the company's approach in that the company derived a minor added benefit for the outcome of social functioning with regard to the 1st improvement by ≥ 10 points.

EORTC QLQ-MY20

For the outcome of health-related quality of life, measured using EORTC QLQ-MY20, the present benefit assessment uses time to 1st deterioration by ≥ 10 points in the individual functioning scales.

None of the EORTC QLQ-MY20 scales on health-related quality of life (body image, future perspective) showed any statistically significant differences between treatment groups. Consequently, there is no hint of added benefit of isatuximab + carfilzomib + dexamethasone in comparison with carfilzomib + dexamethasone for any of them; an added benefit is therefore not proven.

This concurs with the company's approach.

Side effects

SAEs, severe AEs (CTCAE grade ≥ 3)

For the outcomes of SAEs and severe AEs, no statistically significant difference between treatment groups was found. Consequently, there is no hint of greater or lesser harm of isatuximab + carfilzomib + dexamethasone in comparison with carfilzomib + dexamethasone for any of them; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

For discontinuation due to AEs, no usable data are available (see Section 2.4.1 for reasoning). Consequently, there is no hint of greater or lesser harm of isatuximab + carfilzomib + dexamethasone in comparison with carfilzomib + dexamethasone; greater or lesser harm is therefore not proven.

Specific AEs

Infusion-related reactions

For the outcome of infusion-related reactions (operationalized as PT "reaction related to an infusion"), there is a statistically significant difference to the disadvantage of isatuximab + carfilzomib + dexamethasone. Consequently, there is a hint of greater harm of isatuximab + carfilzomib + dexamethasone in comparison with carfilzomib + dexamethasone.

Diseases of the skin and subcutaneous tissue (SOC, AEs)

For the outcome of skin and subcutaneous tissue disorders (SOC, AEs), a statistically significant difference was found to the disadvantage of isatuximab + carfilzomib + dexamethasone. Consequently, there is a hint of greater harm of isatuximab + carfilzomib + dexamethasone in comparison with carfilzomib + dexamethasone.

Thrombocytopoenia (PT, severe AEs)

For the outcome of thrombocytopoenia (PT, severe AEs), a statistically significant difference was found in favour of isatuximab + carfilzomib + dexamethasone. Consequently, there is a hint of lesser harm of isatuximab + carfilzomib + dexamethasone in comparison with carfilzomib + dexamethasone.

The above assessment of the results on the outcome category of AEs departs from that of the company, which did not carry out a derivation of added benefit for specific outcomes. Rather, it derived no hint of greater or lesser harm for the entire outcome category of side effects.

2.4.4 Subgroups and other effect modifiers

For this assessment, the following potential effect modifiers were taken into account:

- Sex (female/male)
- Age (< 65 / ≥ 65 years)
- R-ISS stage at baseline (I or II/III/not classified)

Interaction tests were performed whenever at least 10 patients per subgroup were included in the analysis. For binary data, there must also be 10 events in at least 1 subgroup.

The R-ISS subgroup "not classified" was disregarded for subgroup analyses because the disease stage of patients and distribution within the group were unclear. The results on this subgroup

are presented as supplementary information. If necessary, IQWiG calculations of interaction were carried out for the effect modifier R-ISS stage (I or II versus III) and presented below.

Table 16 shows the results of the subgroup analyses for the comparison of isatuximab + carfilzomib + dexamethasone versus carfilzomib + dexamethasone.

Only results showing an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup. For the EQ-5D VAS responder analyses used in this benefit assessment with time to 1st deterioration by ≥ 15 points, the company did not present any subgroup analyses; therefore, no conclusion can be drawn on general health status with regard to effect modifications.

Table 16: Subgroups (health-related quality of life) – RCT, direct comparison: isatuximab + carfilzomib + dexamethasone vs. carfilzomib + dexamethasone

Study **Outcome** **Characteristic** **Subgroup**	**Isatuximab + carfilzomib + dexamethasone**		**Carfilzomib + dexamethasone**		**Isatuximab + carfilzomib + 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]**
IKEMA						
Health-related quality of life (EORTC QLQ-C30)						
Physical functioning						
Disease stage at baseline (R-ISS)						
I or II	155	6.9 [4.7; 13.2] 98 (63.2)	103	14.8 [6.5; NC] 52 (50.5)	1.31 [0.94; 1.84]	0.112
III	16	NR [9.4; NC] 2 (12.5)	8	1.1 [1.0; NC] 5 (62.5)	0.11 [0.02; 0.62]	0.003
Not classified[c]	*8*	*NR [3.8; NC]* *2 (25.0)*	*12*	*5.9 [3.7; NC]* *8 (66.7)*	*0.37 [0.08; 1.75]*	*0.192*
Total					Interaction[d]:	0.006

a. HR and CI based on proportional hazards model; stratification factors of disease stage at baseline (R-ISS) and interaction between treatment and R-ISS.
b. p-value based on nonstratified log rank test.
c. Due to the unclear allocation to one of the disease stages, this subgroup was disregarded in the analysis on effect modification and presented as supplementary information here.
d. IQWiG calculations; p-value from Q-test for heterogeneity, based on the 2 subgroups "I or II" and "III".

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

Health-related quality of life

EORTC QLQ-C30

Physical functioning

The available subgroup analyses show an effect modification for the outcome of physical functioning by the characteristic of R-ISS stage at baseline.

For patients in R-ISS stage I or II, there is no statistically significant difference between treatment groups. For the subgroup of patients in R-ISS stage I or II, this results in no hint of greater or lesser harm of isatuximab + carfilzomib + dexamethasone versus carfilzomib + dexamethasone.

For patients who were in R-ISS stage III at baseline, a statistically significant difference between treatment groups was found in favour of isatuximab + carfilzomib + dexamethasone versus carfilzomib + dexamethasone. For the subgroup of patients in R-ISS stage III, this results in a hint of added benefit of isatuximab + carfilzomib + dexamethasone versus carfilzomib + dexamethasone.

This departs from the company's approach to the extent that the company did present subgroup analyses but did not take them into account to derive added benefit.

2.5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are presented below. The various outcome categories and the effect sizes have been taken into account. The methods used for this purpose are explained in the IQWiG General Methods [1].

The approach for deriving an overall conclusion on any added benefit by aggregating the conclusions reached at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of added benefit at outcome level

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

Determination of the outcome category for outcomes on symptoms and adverse events

It is not discernible from Module 4 B for all outcomes considered in the present benefit assessment whether they were serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

Symptoms

The IKEMA study recorded symptom outcomes using patient-reported instruments, EORTC QLQ-C30 and EORTC QLY-MY20, and these outcomes were categorized as non-serious/non-severe symptoms / late complications.

This departs from the company's allocation of all patient-reported symptom outcomes to the outcome category of serious/severe symptoms / late complications, without the company providing specific reasoning for this allocation.

Specific AEs

For the specific AEs of infusion-related reactions (operationalized as PT "infusion-related reactions") and diseases of the skin and subcutaneous tissue (SOC, AEs), the majority of events that occurred were non-serious/non-severe, which is why these outcomes were categorized as non-serious/non-severe AEs.

The company did not assess the severity of these outcomes.

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

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Isatuximab + carfilzomib + dexamethasone vs. carfilzomib + dexamethasone** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	NR vs. NR HR: 0.88 [0.52; 1.50]; p = 0.644	Lesser/added benefit not proven
Morbidity		
Symptoms (EORTC QLQ-C30)		
Fatigue	3.8 vs. 4.8 HR: 1.22 [0.92; 1.62]; p = 0.167	Lesser/added benefit not proven
Nausea and vomiting	18.6 vs. NR HR: 1.20 [0.85; 1.70]; p = 0.310	Lesser/added benefit not proven
Pain	7.6 vs. 16.2 HR: 1.26 [0.92; 1.72]; p = 0.144	Lesser/added benefit not proven
Dyspnoea	5.2 vs. 5.8 HR: 1.16 [0.86; 1.56]; p = 0.338	Lesser/added benefit not proven
Insomnia	7.4 vs. 8.4 HR: 1.09 [0.80; 1.48]; p = 0.583	Lesser/added benefit not proven
Appetite loss	14.3 vs. 21.3 HR: 1.18 [0.85; 1.66]; p = 0.322	Lesser/added benefit not proven
Constipation	NR vs. NR HR: 1.12 [0.78; 1.61]; p = 0.536	Lesser/added benefit not proven
Diarrhoea	11.1 vs. NR HR: 1.33 [0.95; 1.86]; p = 0.090	Lesser/added benefit not proven
Symptoms (EORTC QLQ-MY20)		
Symptoms of disease	12.7 vs. 21.6 HR: 1.22 [0.88; 1.69]; p = 0.240	Lesser/added benefit not proven
Side effects	7.4 vs. 13.5 HR: 1.18 [0.87; 1.62]; p = 0.290	Lesser/added benefit not proven

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

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Isatuximab + carfilzomib + dexamethasone vs. carfilzomib + dexamethasone** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Health status (EQ-5D VAS)	NR vs. 16.8 HR: 0.88 [0.62; 1.23]; p = 0.450	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30		
Global health status	5.9 vs. 5.8 HR: 1.19 [0.88; 1.61]; p = 0.255	Lesser/added benefit not proven
Physical functioning Disease stage at baseline (R-ISS) I or II	6.9 vs. 14.8 HR: 1.31 [0.94; 1.84]; p = 0.112	Lesser/added benefit not proven
III	NR vs. 1.1 HR: 0.11 [0.02; 0.62]; p = 0.003 Probability: hint	Outcome category: health-related quality of life $CI_u < 0.75$; risk ≥ 5% Added benefit; extent: major
Role functioning	5.8 vs. 5.8 HR: 1.19 [0.88; 1.61]; p = 0.261	Lesser/added benefit not proven
Emotional functioning	12.9 vs. 16.9 HR: 1.06 [0.76; 1.47]; p = 0.734	Lesser/added benefit not proven
Cognitive functioning	7.8 vs. 7.5 HR: 1.09 [0.81; 1.48]; p = 0.554	Lesser/added benefit not proven
Social functioning	4.7 vs. 4.7 HR: 1.08 [0.81; 1.45]; p = 0.588	Lesser/added benefit not proven
EORTC QLQ-MY20		
Body image	9.0 vs. 20.6 HR: 1.22 [0.88; 1.70]; p = 0.225	Lesser/added benefit not proven
Future perspective	10.6 vs. 8.4 HR: 0.90 [0.66; 1.24]; p = 0.530	Lesser/added benefit not proven

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

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Isatuximab + carfilzomib + dexamethasone vs. carfilzomib + dexamethasone** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
SAEs	12.6 vs. 13.8 HR: 1.08 [0.80; 1.47]; p = 0.616	Greater/lesser harm not proven
Severe AEs	5.6 vs. 6.6 HR: 1.22 [0.93; 1.62]; p = 0.154	Greater/lesser harm not proven
Discontinuation due to AEs	No usable data[c]	Greater/lesser harm not proven
Infusion-related reaction (AEs)[d]	NR vs. NR HR: 17.61 [6.43; 48.19] HR: 0.06 [0.02; 0.16][e] p < 0.001 Probability: hint	Outcome category: non-serious/non-severe AEs $CI_u < 0.80$ greater harm; extent: considerable
Diseases of the skin and subcutaneous tissue (AEs)	NR vs. NR HR: 2.23 [1.26; 3.93] HR: 0.45 [0.25; 0.79][e] p = 0.005 Probability: hint	Outcome category: non-serious/non-severe AEs $CI_u < 0.80$ greater harm; extent: considerable
Thrombocytopoenia (severe AEs)	NR vs. NR 0.26 [0.08; 0.83]; p = 0.015 Probability: hint	Outcome category: serious/severe AEs $0.75 \leq CI_u < 0.90$ Lesser harm; extent: considerable

a. Probability is stated whenever a statistically significant and relevant effect is present.
b. Estimations of effect size are made depending on the outcome category, with different limits according to the upper limit of the confidence interval (CI_u).
c. See Section 2.4.1 for a rationale.
d. Operationalized as PT "infusion-related reaction."
e. IQWiG calculations, reversed direction of effect to enable use of limits to derive the extent of added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; 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 Questionnaire – 5 Dimensions; HR: hazard ratio; NR: not reached; R-ISS: Revised International Staging System; SAE: serious adverse event; VAS: visual analogue scale

2.5.2 Overall conclusion on added benefit

Table 18 summarizes the results which were factored into the overall conclusion on the extent of added benefit.

Table 18: Favourable and unfavourable effects from the assessment of isatuximab + carfilzomib + dexamethasone in comparison with carfilzomib + dexamethasone

Favourable effects	**Unfavourable effects**
Health-related quality of life ▪ Physical functioning ▫ Disease stage at baseline (R-ISS) (III) hint of added benefit – extent: major	–
–	Non-serious/non-severe AEs ▪ Infusion-related reactions (PT "infusion-related reaction"): hint of greater harm – extent: considerable ▪ Skin and subcutaneous tissue disorders: hint of greater harm – extent: considerable
Serious/severe AEs ▪ Thrombocytopoenia (severe AEs): hint of lesser harm – extent: considerable	–
Data on the outcome of discontinuation due to AEs (≥ 1 drug component) are missing.	
AEs: adverse events; R-ISS: Revised International Staging System	

Overall, both favourable and unfavourable effects of different extents are found for isatuximab + carfilzomib + dexamethasone in comparison with carfilzomib + dexamethasone, all with the probability of hint. They concern both the outcome of health-related quality of life and outcomes on side effects of different severities.

The favourable effects concern physical functioning in the category of health-related quality of life as well as the outcome of thrombocytopoenia in the serious/severe adverse events category. For the outcome of physical functioning, the favourable effect is limited to patients in disease stage R-ISS III, where there is a hint of major added benefit. For the outcome of thrombocytopoenia, there is a hint of lesser harm with an extent of considerable for the entire target population.

All of the unfavourable effects are for specific AEs from the outcome category of non-serious/non-severe AEs. For the outcomes of infusion-related reactions (PT) as well as skin and subcutaneous tissue disorders, a hint of greater harm of considerable extent was shown for isatuximab + carfilzomib + dexamethasone versus carfilzomib + dexamethasone.

The effect modification by disease stage (R-ISS) at baseline, which was observed in only 1 outcome on health-related quality of life, does not justify a separate conclusion on added benefit for different patient groups.

Overall, the distribution of favourable and unfavourable effects is deemed balanced, given the fact that the unfavourable effects are from the outcome category non-serious/non-severe side effects. In summary, there is therefore no proof of added benefit of isatuximab + carfilzomib +

dexamethasone versus carfilzomib + dexamethasone in patients with multiple myeloma who received at least 1 prior therapy.

Table 19 presents a summary of the results of the benefit assessment of isatuximab + carfilzomib + dexamethasone in comparison with the ACT.

Table 19: Isatuximab + carfilzomib + 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[b]	▪ 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**.
b. According to the G-BA, it is assumed that high-dose chemotherapy with stem cell transplantation is not an option for the patients at the time of the current therapy.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The above assessment deviates from that by the company, which claimed an indication of considerable added benefit.

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

References for English extract

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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