Isatuximab (multiple myeloma)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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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.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by Hans Josef van Lier.

IQWiG thanks the respondent and the patient organization “Plasmozytom / Multiples Myelom NRW” for participating in the written exchange and for their support. The respondent and “Plasmozytom / Multiples Myelom NRW” were not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

I Table of contents

I List of tables[2]

Page

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AESI	adverse event of special interest
ASCT	autologous stem cell transplant
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DGHO	Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (German Society for Haematology and Medical Oncology)
ECOG PS	Oncology Group Performance Status
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IMWG	International Myeloma Working Group
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IRC	independent review committee
MedDRA	Medical Dictionary for Regulatory Activities
PFS	progression-free survival
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-MY20	Quality of Life Questionnaire-Myeloma Module 20
R-ISS	Revised International Staging System
RCT	randomized controlled trial
RKI	Robert Koch Institute
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SPC	Summary of Product Characteristics

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book 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 bortezomib, lenalidomide and dexamethasone). The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 11 February 2025.

Research question

The aim of this report is to assess the added benefit of isatuximab in combination with bortezomib, lenalidomide and dexamethasone (hereinafter "isatuximab + bortezomib + lenalidomide + dexamethasone") in comparison with the appropriate comparator therapy (ACT) in patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (ASCT).

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of isatuximab + bortezomib + lenalidomide + dexamethasone

Therapeutic indication	**ACT**[a]
Adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant	▪ daratumumab in combination with lenalidomide and dexamethasone, or ▪ daratumumab in combination with bortezomib, melphalan and prednisone, or ▪ bortezomib in combination with melphalan and prednisone, or ▪ bortezomib in combination with lenalidomide and dexamethasone, or ▪ thalidomide in combination with melphalan and prednisone, or ▪ bortezomib in combination with cyclophosphamide and dexamethasone (only for patients with peripheral polyneuropathy or an increased risk of developing peripheral polyneuropathy[b])
a. Presented is the ACT specified by the G-BA. b. See Appendix VI to Section K of the Pharmaceutical Directive. G-BA: Federal Joint Committee	

The company followed the specification of the ACT.

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 to derive the added benefit.

Study pool and study design

Concurring with the company, the study pool for the benefit assessment consisted of the IMROZ study. However, there were uncertainties regarding the unsuitability of ASCT for the patients included (see below).

IMROZ study

The IMROZ study is an ongoing, open-label RCT comparing isatuximab + bortezomib + lenalidomide + dexamethasone versus bortezomib + lenalidomide + dexamethasone.

The study included patients ≥ 18 and ≤ 80 years of age with newly diagnosed multiple myeloma, as defined by the International Myeloma Working Group (IMWG) criteria, who were ineligible for high-dose chemotherapy followed by ASCT. According to the inclusion criteria, ASCT was not an option for patients who were aged ≥ 65 years, or who were aged < 65 years and had important comorbidities.

The IMROZ study was divided into a global cohort and a China expansion cohort. The global cohort included a total of 446 patients, randomized in a 3:2 ratio to treatment with either isatuximab + bortezomib + lenalidomide + dexamethasone (N = 265) or bortezomib + lenalidomide + dexamethasone (N = 181). A total of 12 Chinese patients were included in the global cohort and 38 Chinese patients (corresponding to 7.9% of the total study population) in the China expansion cohort. In Module 4 C, the company presented analyses for the global cohort, which did not include the 38 Chinese patients from the China expansion cohort. This was not relevant for this benefit assessment, as the proportion of Chinese patients from the China expansion cohort was low.

The IMROZ study was divided into 2 treatment phases. In the induction phase (4 cycles of 42 days each), patients were treated with either isatuximab + bortezomib + lenalidomide + dexamethasone or bortezomib + lenalidomide + dexamethasone. In the subsequent maintenance phase from Cycle 5 (cycle length of 28 days), bortezomib was discontinued as part of the study medication and patients continued treatment with isatuximab + lenalidomide + dexamethasone or lenalidomide + dexamethasone.

Treatment in the intervention arm with isatuximab + bortezomib + lenalidomide + dexamethasone and in the comparator arm with bortezomib + lenalidomide + dexamethasone was largely in compliance with the Summary of Product Characteristics (SPC).

Treatment with the study medication was continued until disease progression according to IMWG criteria or until other discontinuation criteria were met, such as toxicity or patient decision. In addition, patients with confirmed disease progression could switch from the comparator arm to treatment with isatuximab + lenalidomide + dexamethasone at the

investigator's discretion during the maintenance phase if no other systemic cancer therapy had been administered.

The IMROZ study's primary outcome was progression-free survival (PFS) according to a blinded independent review committee (IRC). Patient-relevant secondary outcomes included outcomes in the categories of mortality, morbidity, health-related quality of life and side effects.

Data cuts

The results of the first data cut (for the outcome categories mortality, morbidity and health-related quality of life from 26 September 2023, and for side effects from 3 October 2023) were used for this benefit assessment.

Uncertainties regarding the IMROZ study – ASCT ineligibility of the study population questionable

According to the inclusion criteria of the IMROZ study, ASCT was not considered an option for patients who were at least 65 years of age, or who were younger than 65 years and had important comorbidities. According to the current guideline recommendation age is not a suitable criterion to operationalize the ineligibility for ASCT, however. Biological age in good general health is currently considered more important than chronological age when assessing eligibility for ASCT. It is difficult to define a maximum age for ASCT. Instead, individual patient factors should be considered when making treatment decisions, taking into account the patient's general condition, existing comorbidities, functional status and social integration. For the operationalization of ASCT ineligibility, it is therefore not appropriate to determine patient ineligibility for ASCT solely on the basis of age (≥ 65 years), as was done in the IMROZ study.

In Module 4 C, the company addressed the operationalization of ASCT ineligibility in the IMROZ study with reference to the approval procedure for daratumumab, where the European Medicines Agency (EMA) criticized the inadequate inclusion criteria for representing the population to be assessed. Therefore, as an approximation to a population that is ineligible for ASCT, the company presented post hoc analyses for the subpopulation "ASCT ineligibility as per the EMA definition" (hereinafter referred to as "subpopulation") as a sensitivity analysis. In the IMROZ study, 74% of the patients included in the global cohort (hereinafter referred to as the total population) fulfilled the criteria for forming the subpopulation. However, there was the uncertainty for both the total population and for the subpopulation defined post hoc as to the proportion of patients who would have in fact been ineligible for ASCT. The assessment of ASCT ineligibility should be patient-specific and independent of chronological age. However, the assessment for the IMROZ study was not carried out in this way, and the corresponding information can no longer be determined post hoc.

Approach of the company and consequences for the benefit assessment

According to the General Methods of the Institute, studies that do not completely fulfil an inclusion criterion of the research question of interest are included in the benefit assessment if the criterion is fulfilled in at least 80% of the (sub)population of interest of the study. Regardless of the degree of fulfilment (at least 80%, less than 80%), there may be situations in which there is suitable information on an effect modification by the inclusion criterion in question (population or interventions). In these situations, a decision must be made on whether to include the study based on the strength of the effect modification and the proportion of patients who do not meet the inclusion criterion or the degree of deviation of the interventions. In the present case, the subpopulation comprised 74% of the total population, but the operationalization was subject to uncertainty (see above). It is therefore also conceivable that more than 80% of the total population of the IMROZ study were ineligible for ASCT, concurring with the target population of the research question. However, there were effect modifications from the characteristic ASCT ineligibility/eligibility (subgroups presented by the company: ASCT ineligibility according to EMA criteria versus remaining patients in the total population) as well as relevant differences in the results for these subgroups in outcomes relevant to the conclusion, such as symptoms (recorded using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30] – nausea and vomiting functional scale), severe adverse events (AEs) (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3) and serious AEs (SAEs). In addition, there were opposing effects between the ASCT eligibility/ineligibility subgroups across several outcomes, e.g. the outcome constipation recorded using the EORTC QLQ-C30.

Overall, there were relevant differences in the results of outcomes relevant to the conclusion for the subgroups ASCT ineligibility/eligibility, so that the total population of the IMROZ study could not be used in the context of this benefit assessment. Instead, the subpopulation formed by the company was used, as this represented a better approximation of the target population. However, the subpopulation was also subject to uncertainty (see above). Although this uncertainty did not fundamentally call into question the suitability of the IMROZ study and the consideration of the subpopulation, it was taken into account in the certainty of conclusions.

Risk of bias

The risk of bias across outcomes was assessed as low for the IMROZ study.

The risk of bias of the result on the outcome of overall survival was rated as low. The risk of bias of the results was rated as high for the outcomes on symptoms (recorded using the EORTC QLQ-C30 and the EORTC Quality of Life Questionnaire-Myeloma 20 [QLQ-MY20]), health status (recorded using the EQ-5D VAS) and on health-related quality of life (recorded using

the EORTC QLQ-C30 and the EORTC QLQ-MY20), as well as for the outcomes in the side effects category (SAEs, severe AEs and the specific AEs metabolism and nutrition disorders [System Organ Class [SOC], severe AEs] and respiratory, thoracic and mediastinal disorders [SOC, severe AEs]).

No (suitable) analyses were available for the outcomes discontinuation due to AEs, infusion-related reactions and peripheral neuropathy. The risk of bias for these outcomes was therefore not assessed.

Irrespective of the aspects described under the risk of bias, the certainty of conclusions of the study results was in principle limited due to the described uncertainties regarding ASCT ineligibility of the relevant subpopulation included. The IMROZ study can therefore at most be used to derive hints, for example of an added benefit.

Results

Mortality

Overall survival

There was no statistically significant difference between the treatment arms for the outcome overall survival. There was no hint of an added benefit of isatuximab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone; an added benefit is therefore not proven.

Morbidity

Symptoms (EORTC QLQ-C30)

Dyspnoea

A statistically significant difference in favour of isatuximab + bortezomib + lenalidomide + dexamethasone was shown for the outcome dyspnoea. There is a hint of an added benefit of isatuximab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone.

Nausea and vomiting, appetite loss

A statistically significant difference in favour of isatuximab + bortezomib + lenalidomide + dexamethasone was shown for the outcomes nausea and vomiting, and appetite loss. However, the difference was no more than marginal for these outcomes in the category of non-serious/non-severe symptoms/late complications. In either case, there was no hint of an added benefit of isatuximab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone; an added benefit is therefore not proven for either outcome.

Fatigue, pain, insomnia, constipation and diarrhoea

No statistically significant difference between the treatment arms was shown for any of the outcomes fatigue, pain, insomnia, constipation and diarrhoea. In each case, there was no hint of an added benefit of isatuximab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone; an added benefit is therefore not proven for these outcomes.

EORTC QLQ-MY20

Disease symptoms and side effects

There was no statistically significant difference between the treatment arms for either of the outcomes disease symptoms and side effects. In each case, there was no hint of an added benefit of isatuximab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone; an added benefit is therefore not proven for these outcomes.

Health status (EQ-5D VAS)

No statistically significant difference between the treatment arms was shown for the outcome health status, recorded using the EQ-5D VAS. There was no hint of an added benefit of isatuximab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

Role functioning

A statistically significant difference in favour of isatuximab + bortezomib + lenalidomide + dexamethasone was shown for the outcome role functioning. There is a hint of an added benefit of isatuximab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone.

Global health status, physical functioning, emotional functioning, cognitive functioning and social functioning

No statistically significant difference between the treatment arms was shown for any of the outcomes global health status, physical functioning, emotional functioning, cognitive functioning and social functioning. In each case, there was no hint of an added benefit of isatuximab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone; an added benefit is therefore not proven for these outcomes.

EORTC QLQ-MY20

Future perspective

A statistically significant difference in favour of isatuximab + bortezomib + lenalidomide + dexamethasone was shown for the outcome future perspective. There is a hint of an added benefit of isatuximab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone.

Body image

No statistically significant difference between the treatment arms was shown for the outcome body image. There was no hint of an added benefit of isatuximab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone; an added benefit is therefore not proven.

Side effects

SAEs and severe AEs

There was no statistically significant difference between the treatment arms for the outcomes of SAEs and severe AEs. In either case, there was no hint of greater or lesser harm from isatuximab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone; greater or lesser harm is therefore not proven for either of the outcomes.

Discontinuation due to AEs and infusion-related reactions

The analyses presented by the company for the outcomes discontinuation due to AEs and infusion-related reactions were not suitable for the benefit assessment. In either case, there was no hint of greater or lesser harm from isatuximab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone; greater or lesser harm is therefore not proven for either of the outcomes.

Peripheral neuropathy

No analyses for the relevant subpopulation were available for the outcome peripheral neuropathy. There was no hint of greater or lesser harm from isatuximab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone; greater or lesser harm is therefore not proven.

Metabolism and nutrition disorders (SOC, severe AEs) and respiratory, thoracic and mediastinal disorders (SOC, severe AEs)

For each of the outcomes metabolism and nutrition disorders (SOC, severe AEs) and respiratory, thoracic and mediastinal disorders (SOC, severe AEs), there was a statistically significant difference to the advantage of isatuximab + bortezomib + lenalidomide +

dexamethasone. There was a hint of lesser harm of isatuximab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + 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 isatuximab + bortezomib + lenalidomide + dexamethasone in comparison with the ACT is assessed as follows:

Overall, only positive effects of varying extent were shown for isatuximab + bortezomib + lenalidomide + dexamethasone.

For each of the patient-reported outcomes on symptoms (dyspnoea) and health-related quality of life (role functioning and future perspective), there was a hint of an added benefit of minor extent. In addition, for 2 specific AEs in the category of serious/severe side effects, there was a hint of lesser harm of considerable or major extent. However, no suitable data were available for the outcome discontinuation due to AEs, infusion-related reactions and for the outcome peripheral neuropathy. Furthermore, the symptoms underlying the infusion-related reactions were not included in the analyses of AEs, so that further disadvantages in the specific AEs were potentially overlooked.

In summary, there was a hint of minor added benefit of isatuximab + bortezomib + lenalidomide + dexamethasone versus bortezomib + lenalidomide + dexamethasone for patients with newly diagnosed multiple myeloma who are ineligible for ASCT.

Table 3 shows a summary of the probability and extent of the added benefit of isatuximab + bortezomib + lenalidomide + 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: Isatuximab + bortezomib + lenalidomide + dexamethasone – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant	▪ daratumumab in combination with lenalidomide and dexamethasone, or ▪ daratumumab in combination with bortezomib, melphalan and prednisone, or ▪ bortezomib in combination with melphalan and prednisone, or ▪ bortezomib in combination with lenalidomide and dexamethasone, or ▪ thalidomide in combination with melphalan and prednisone, or ▪ bortezomib in combination with cyclophosphamide and dexamethasone (only for patients with peripheral polyneuropathy or an increased risk of developing peripheral polyneuropathy[b])	Hint of minor added benefit[c]

a. Presented is the ACT specified by the G-BA.
b. See Appendix VI to Section K of the Pharmaceutical Directive.
c. Only patients with an ECOG PS of 0 to 2 were included in the IMROZ study. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of > 2.

ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee

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

I 2 Research question

The aim of this report is to assess the added benefit of isatuximab in combination with bortezomib, lenalidomide and dexamethasone (hereinafter "isatuximab + bortezomib + lenalidomide + dexamethasone") in comparison with the ACT in patients with newly diagnosed multiple myeloma who are ineligible for ASCT.

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of isatuximab + bortezomib + lenalidomide + dexamethasone

Therapeutic indication	**ACT**[a]
Adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant	▪ daratumumab in combination with lenalidomide and dexamethasone, or ▪ daratumumab in combination with bortezomib, melphalan and prednisone, or ▪ bortezomib in combination with melphalan and prednisone, or ▪ bortezomib in combination with lenalidomide and dexamethasone, or ▪ thalidomide in combination with melphalan and prednisone, or ▪ bortezomib in combination with cyclophosphamide and dexamethasone (only for patients with peripheral polyneuropathy or an increased risk of developing peripheral polyneuropathy[b])
a. Presented is the ACT specified by the G-BA. b. See Appendix VI to Section K of the Pharmaceutical Directive. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the specification of the ACT.

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 to derive the added benefit. This concurs with the company's inclusion criteria.

I 3 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study list on isatuximab (status: 3 December 2024)
- Bibliographical literature search on isatuximab (last search on 3 December 2024)
- Search of trial registries/trial results databases for studies on isatuximab (last search on 3 December 2024)
- Search on the G-BA website for isatuximab (last search on 4 December 2024)

To check the completeness of the study pool:

- Search of trial registries for studies on isatuximab (last search on 26 February 2025); for search strategies, see I Appendix A of the full dossier assessment

The search did not identify any additional relevant studies.

I 3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: isatuximab + bortezomib + lenalidomide + dexamethasone[a] vs. bortezomib + lenalidomide + dexamethasone[b]

Study	Study category			Available sources		
	Study for the marketing authorization of the drug to be assessed (yes/no)	Sponsored study[c] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[d] (yes/no [citation])	Publication (yes/no [citation])
EFC12522 (IMROZ[e])	Yes	Yes	No	Yes [3,4]	Yes [5-7]	Yes [8]

a. Followed by treatment with isatuximab + lenalidomide + dexamethasone in the maintenance phase (Cycle 5 and later).
b. Followed by treatment with lenalidomide + dexamethasone in the maintenance phase (Cycle 5 and later).
c. Study sponsored by the company.
d. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
e. In the following tables, the study is referred to by this acronym.

CSR: clinical study report; RCT: randomized controlled trial

Concurring with the company, the IMROZ study was included in the benefit assessment. However, there were uncertainties regarding the unsuitability of ASCT for the patients

included. These uncertainties and their effect on this benefit assessment are described in Sections I 3.2 and I 4.2.

I 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: isatuximab + bortezomib + lenalidomide + dexamethasone[a] vs. bortezomib + lenalidomide + dexamethasone[b] (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[c]
IMROZ	RCT, open-label, parallel	Adult patients (≥ 18 years and ≤ 80 years) with newly diagnosed multiple myeloma ▪ who are ineligible for high-dose chemotherapy with stem cell transplantation (age ≥ 65 years, or < 65 years with important comorbidities) ▪ ECOG PS ≤ 2	isatuximab + bortezomib + lenalidomide + dexamethasone[a] (N = 265) bortezomib + lenalidomide + dexamethasone[b] (N = 181) Relevant subpopulation thereof[d]: isatuximab + bortezomib + lenalidomide + dexamethasone[a] (n = 196) bortezomib + lenalidomide + dexamethasone[b] (n = 136)	Screening: ≤ 28 days Treatment: until disease progression[e], unacceptable toxicity Observation[f]: outcome-specific, at most until death or end of study[g]	96 centres in Australia, Belgium, China, Czech Republic, Denmark, France, Germany, Greece, Italy, Japan, Lithuania, Mexico, New Zealand, Poland, Portugal, Russia, Spain, Sweden, Taiwan, Turkey, United States 12/2017–ongoing Data cut-offs: 26 Sep 2023 (interim analysis[h])	Primary: PFS Secondary: overall survival, morbidity, health-related quality of life, AEs

a. Followed by treatment with isatuximab + lenalidomide + dexamethasone in the maintenance phase (Cycle 5 and later).
b. Followed by treatment with lenalidomide + dexamethasone in the maintenance phase (Cycle 5 and later).
c. 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.
d. Patients who are ineligible for ASCT, defined as patients aged < 65 years with important comorbidities, patients aged ≥ 65 and ≤ 69 years with ECOG PS = 2, and patients aged ≥ 70 years.
e. Patients with confirmed disease progression in the comparator arm could receive isatuximab in addition to lenalidomide + dexamethasone at the investigator's discretion during the maintenance phase if no other systemic cancer therapy had been administered. Treatment was continued until disease progression or unacceptable toxicity. At the data cut-off on 26 September 2023, 25 patients in the comparator arm had received isatuximab + lenalidomide + dexamethasone.
f. Outcome-specific information is provided in Table 8.
g. From Amendment 6 (10 June 2022), the end of the study as per the study protocol is on the data cut-off date of the prespecified final analysis of overall survival (planned for after approximately 202 deaths).
h. Prespecified interim analysis after 162 PFS events in the total population (planned for after 167 events, when 75% of PFS events were observed).

Table 6: Characteristics of the study included – RCT, direct comparison: isatuximab + bortezomib + lenalidomide + dexamethasone[a] vs. bortezomib + lenalidomide + dexamethasone[b] (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[c]
AE: adverse event; ASCT: autologous stem cell transplantation; ECOG PS: Eastern Cooperative Oncology Group Performance Status; N: number of randomized patients; n: relevant subpopulation; PFS: progression-free survival; RCT: randomized controlled trial						

Table 7: Characteristics of the intervention – RCT, direct comparison: isatuximab + bortezomib + lenalidomide + dexamethasone[a] vs. bortezomib + lenalidomide + dexamethasone[b] (multipage table)

Study	Intervention	Comparison[c]
IMROZ	isatuximab 10 mg/kg BW IV ▪ Cycle 1[d]: Days 1, 8, 15, 22 and 29 ▪ Cycles 2–4[d]: Days 1, 15 and 29 ▪ Cycles 5–17[e]: Days 1 and 15 ▪ Starting with Cycle 18[e]: once per cycle + bortezomib 1.3 mg/m² BSA, SC ▪ Cycles 1–4[d]: Days 1, 4, 8, 11, 22, 25, 29, 32 + lenalidomide 25 mg[f] orally ▪ Cycles 1–4[d]: Days 1 to 14 and Days 22 to 35 ▪ Starting with Cycle 5[e]: Days 1 to 21 + dexamethasone 20 mg orally or IV[g] ▪ Cycles 1–4[d]: Days 1, 2, 4, 5, 8, 9, 11, 12, 15, 22, 23, 25, 26, 29, 30, 32 and 33[h] ▪ Starting with Cycle 5[e]: Days 1, 8, 15 and 22	bortezomib 1.3 mg/m² BSA, SC ▪ Cycles 1–4[d]: Days 1, 4, 8, 11, 22, 25, 29, 32 + lenalidomide 25 mg orally ▪ Cycles 1–4[d]: Days 1 to 14 and Days 22 to 35 ▪ Starting with Cycle 5[e]: Days 1 to 21 + dexamethasone 20 mg orally[g] ▪ Cycles 1–4[d]: Days 1, 2, 4, 5, 8, 9, 11, 12, 15, 22, 23, 25, 26, 29, 30, 32 and 33[h] ▪ Starting with Cycle 5[e]: Days 1, 8, 15 and 22
	Treatment adjustments ▪ Isatuximab: dose reduction not permitted ▪ Bortezomib, lenalidomide, dexamethasone: gradual dose reductions allowed as per the study protocol[i] ▪ ≥ 1 dose of one or several treatment components within one cycle could be omitted due to toxicity as per the study protocol[j] ▪ Treatment with the remaining drug components could be continued after discontinuation of a drug component.	
	Disallowed pretreatment ▪ Prior or current systemic therapy or stem cell transplantation for multiple myeloma[k] **Concomitant treatment** <u>Required</u> ▪ Premedication before isatuximab infusion[l]: paracetamol 650–1000 mg orally; ranitidine 50 mg IV (or equivalent); diphenhydramine 25–50 mg IV (or equivalent) and dexamethasone (see above for dosage) <u>Allowed</u> ▪ Palliative radiotherapy for pain relief (< 20% of the bone marrow within a 3-week period) ▪ Glucocorticoids, antihistamines and analgesics for the management of infusion-related reactions, as well as inhaled glucocorticoids if indicated ▪ Prophylactic administration of G-CSF in patients with recurrent neutropenia or with serious neutropenic complications (e.g. sepsis) <u>Disallowed</u> ▪ Other antineoplastic myeloma therapies ▪ Systemic corticosteroids other than as part of the protocol-specified study treatment or for treatment of hypersensitivity reactions	

Table 7: Characteristics of the intervention – RCT, direct comparison: isatuximab + bortezomib + lenalidomide + dexamethasone[a] vs. bortezomib + lenalidomide + dexamethasone[b] (multipage table)

Study	Intervention	Comparison[c]
a. Followed by treatment with isatuximab + lenalidomide + dexamethasone in the maintenance phase (Cycle 5 and later). b. Followed by treatment with lenalidomide + dexamethasone in the maintenance phase (Cycle 5 and later). c. Patients with confirmed disease progression in the comparator arm could receive isatuximab in addition to lenalidomide + dexamethasone at the investigator's discretion during the maintenance phase (starting with Cycle 5) if no other systemic cancer therapy had been administered. Patients who permanently discontinued lenalidomide and dexamethasone were not allowed to switch to subsequent treatment with isatuximab + lenalidomide + dexamethasone. d. Induction phase: 42 ± 3 days per cycle. e. Maintenance phase: 28 ± 3 days per cycle. f. Lenalidomide 10 mg/day for patients with creatinine clearance ≥ 30 to < 60 mL/min. g. Dexamethasone was administered IV on the days when isatuximab was administered and orally on the other days. For the comparator arm, it is unclear whether dexamethasone was generally administered orally or whether it was also administered intravenously on the days when isatuximab was administered in the intervention arm. h. Patients aged ≥ 75 years received dexamethasone on Days 1, 4, 8, 11, 15, 22, 25, 29 and 32. i. If the dose was reduced, a further dose increase was not permitted unless the patient was treated with isatuximab in addition to lenalidomide + dexamethasone at the investigator's discretion after confirmed disease progression, and the dose had not previously been reduced due to toxicity. j. If there was no improvement in toxicity according to the study protocol, the next cycle could be delayed for ≤ 14 days. If there was no improvement within this period, the study treatment was to be discontinued at the investigator's discretion and in consultation with the sponsor. k. Emergency use of corticosteroids for ≤ 14 days before randomization (equivalent to dexamethasone 40 mg/day for 4 days) was allowed. l. Premedication was recommended according to the sequence shown. If no infusion-related reactions occurred after 4 consecutive administrations of isatuximab, the investigator could reconsider the need for isatuximab-specific premedication. G-CSF: granulocyte colony-stimulating factor; BSA: body surface area; BW: body weight; IV: intravenous; RCT: randomized controlled trial; SC: subcutaneous		

IMROZ study

The IMROZ study is an ongoing, open-label RCT comparing isatuximab + bortezomib + lenalidomide + dexamethasone versus bortezomib + lenalidomide + dexamethasone.

The study included patients ≥ 18 and ≤ 80 years of age with newly diagnosed multiple myeloma, as defined by the IMWG criteria, who were ineligible for high-dose chemotherapy followed by ASCT. According to the inclusion criteria, ASCT was not an option for patients who were aged ≥ 65 years, or who were aged < 65 years and had important comorbidities (see also the following section on uncertainties regarding the IMROZ study and Section I 4.2). In addition, the patients' general health at enrolment had to correspond to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 2.

The IMROZ study was divided into a global cohort and a China expansion cohort. The global cohort included a total of 446 patients, randomized in a 3:2 ratio to treatment with either isatuximab + bortezomib + lenalidomide + dexamethasone (N = 265) or bortezomib + lenalidomide + dexamethasone (N = 181). Randomization was stratified by the characteristics country (non-China versus China), age (< 70 years versus ≥ 70 years) and Revised International Staging System (R-ISS) stage (I or II versus III versus not classified). After completion of recruitment to the global cohort, randomization remained open for the China expansion cohort until a total of N = 50 Chinese patients were enrolled. A total of 12 Chinese patients were included in the global cohort and 38 Chinese patients (corresponding to 7.9% of the total study population) in the China expansion cohort. A separate clinical study report (CSR) for the entire Chinese subpopulation is available in the study documents. In Module 4 C, the company presented analyses for the global cohort, which did not include the 38 Chinese patients from the China expansion cohort. This was not relevant for this benefit assessment, as the proportion of Chinese patients from the China expansion cohort was low.

The IMROZ study was divided into 2 treatment phases. In the induction phase (4 cycles of 42 days each), patients were treated with either isatuximab + bortezomib + lenalidomide + dexamethasone or bortezomib + lenalidomide + dexamethasone. In the subsequent maintenance phase from Cycle 5 (cycle length of 28 days), bortezomib was discontinued as part of the study medication and patients continued treatment with isatuximab + lenalidomide + dexamethasone or lenalidomide + dexamethasone.

Treatment in the intervention arm with isatuximab + bortezomib + lenalidomide + dexamethasone and in the comparator arm with bortezomib + lenalidomide + dexamethasone was largely in compliance with the SPC [9-12]. In the intervention arm, patients received a premedication before treatment with isatuximab to prevent infusion-related reactions. As part of the premedication, patients were treated with H2 antagonists (50 mg ranitidine or other H2 antagonists, such as cimetidine) or proton pump inhibitors, among others, at the discretion of the investigator. In the global cohort, around 80% of the patients in the intervention arm received concomitant medication with these drugs (mainly ranitidine), but it remains unclear whether their administration as part of the premedication for isatuximab was in compliance with the SPC. Against the background of the high proportion of patients with such concomitant medication, however, this had no consequences for the benefit assessment. It should be noted that the marketing authorization for ranitidine-containing drugs is currently suspended in Germany [13]. In contrast to the intervention arm, dexamethasone was initially not administered on Day 15 during the induction phase in the comparator arm. The number of treatment days (per cycle) with dexamethasone was only harmonized between the study arms with Amendment 2 of the study protocol from 12 March 2018. It is assumed that this deviation had no relevant effects, as the proportion of the missing dexamethasone dose per cycle is small in relation to the total dose per cycle (1 dose out of a total of 17 doses per cycle).

Treatment with the study medication was continued until disease progression according to IMWG criteria or until other discontinuation criteria were met, such as toxicity or patient decision. In addition, patients with confirmed disease progression could switch from the comparator arm to treatment with isatuximab + lenalidomide + dexamethasone at the investigator's discretion during the maintenance phase if no other systemic cancer therapy had been administered. Patients who permanently discontinued lenalidomide and dexamethasone were not allowed to switch to subsequent treatment with isatuximab + lenalidomide + dexamethasone.

The IMROZ study's primary outcome was PFS according to a blinded IRC. Patient-relevant secondary outcomes included outcomes in the categories of mortality, morbidity, health-related quality of life and side effects.

Data cuts

The IMROZ study is an ongoing study. The study protocol specified a final analysis of PFS after 222 events as well as 3 interim analyses (after 60%, 75% and 85% of the 222 PFS events). According to the information provided by the company in Module 4 C, no analysis was conducted for the first interim analysis. Thus, the first data cut-off was conducted at the time of the planned second interim analysis after the occurrence of approx. 75% of the 222 PFS events (for the outcome categories mortality, morbidity and health-related quality of life from 26 September 2023, and for side effects from 3 October 2023). This data cut was used for the present benefit assessment. The final data cut-off for analysis of the overall survival outcome was planned for after approx. 202 deaths.

Uncertainties regarding the IMROZ study – ASCT ineligibility of the study population questionable

The therapeutic indication of isatuximab + bortezomib + lenalidomide + dexamethasone to be assessed includes patients with newly diagnosed multiple myeloma who are ineligible for ASCT. According to the inclusion criteria of the IMROZ study, ASCT was not considered an option for patients who were at least 65 years of age, or who were younger than 65 years and had important comorbidities. According to the current guideline recommendation [14] age is not a suitable criterion to operationalize the ineligibility for ASCT, however. Biological age in good general health is currently considered more important than chronological age when assessing eligibility for ASCT. It is difficult to define a maximum age for ASCT. Instead, individual patient factors should be considered when making treatment decisions, taking into account the patient's general condition, existing comorbidities, functional status and social integration [14]. For the operationalization of ASCT ineligibility, it is therefore not appropriate to determine patient ineligibility for ASCT solely on the basis of age (≥ 65 years), as was done in the IMROZ study.

In Module 4 C, the company addressed the operationalization of ASCT ineligibility in the IMROZ study with reference to the approval procedure for daratumumab, where the EMA criticized the inadequate inclusion criteria for representing the population to be assessed. Therefore, as an approximation to a population that is ineligible for ASCT, the company presented post hoc analyses for the subpopulation "ASCT ineligibility as per the EMA definition" (hereinafter referred to as "subpopulation") as a sensitivity analysis. To form the subpopulation, the company chose the same operationalization that had already been used in dossier assessments A18-66 [15] and A23-127 [16] on daratumumab. This subpopulation included the following patients:

- Age < 65 years with important comorbidities
- Age 65 – 69 years with ECOG PS = 2
- Age ≥ 70 years regardless of comorbidities or ECOG status

In the IMROZ study, 74% of the patients included in the global cohort (hereinafter referred to as the total population) fulfilled these criteria. Module 4 C did not provide complete information on how the patients in the subpopulation were distributed across the 3 criteria. However, the information on the characteristic of age showed that the subpopulation mainly included patients ≥ 70 years of age (93%) (see Table 9). The chosen procedure for operationalization of the subpopulation (ASCT ineligibility) is comprehensible and is considered an approximation of the target population. However, there was the uncertainty for both the total population and for the subpopulation defined post hoc as to the proportion of patients who would have in fact been ineligible for ASCT. The assessment of ASCT ineligibility should be patient-specific and independent of chronological age. However, the assessment for the IMROZ study was not carried out in this way, and the corresponding information can no longer be determined post hoc.

Approach of the company and consequences for the benefit assessment

In Module 4 C, the company described that the results shown for the post-hoc operationalized subpopulation described above as well as for the total population were sufficiently comparable across all outcomes, so that a relevant influence of the change in the criteria for the suitability of an ASCT on the results of the IMROZ study can be excluded. Consequently, the company used the total population of the IMROZ study for the benefit assessment of isatuximab.

According to the General Methods of the Institute [1], studies that do not fully meet an inclusion criterion of the research question of interest are included in the benefit assessment if the criterion is fulfilled in at least 80% of the (sub)population of interest of the study. Regardless of the degree of fulfilment (at least 80%, less than 80%), there may be situations in which there is suitable information on an effect modification by the inclusion criterion in

question (population or interventions). In these situations, a decision must be made on whether to include the study based on the strength of the effect modification and the proportion of patients who do not meet the inclusion criterion or the degree of deviation of the interventions. In the present case, the subpopulation comprised 74% of the total population, but the operationalization was subject to uncertainty (see above). It is therefore also conceivable that more than 80% of the total population of the IMROZ study were ineligible for ASCT, concurring with the target population of the research question. However, there were effect modifications from the characteristic ASCT ineligibility/eligibility (subgroups presented by the company: ASCT ineligibility according to EMA criteria versus remaining patients in the total population) as well as relevant differences in the results for these subgroups in outcomes relevant to the conclusion, such as symptoms (recorded using the EORTC QLQ-C30 – nausea and vomiting functional scale), severe AEs (CTCAE] grade ≥ 3 and SAEs. In addition, there were opposing effects between the ASCT eligibility/ineligibility subgroups across several outcomes, e.g. the outcome constipation recorded using the EORTC QLQ-C30.

Overall, there were relevant differences in the results of outcomes relevant to the conclusion for the subgroups ASCT ineligibility/eligibility, so that the total population of the IMROZ study could not be used in the context of this benefit assessment. Instead, the subpopulation formed by the company was used, as this represented a better approximation of the target population. However, the subpopulation was also subject to uncertainty (see above). Although this uncertainty did not fundamentally call into question the suitability of the IMROZ study and the consideration of the subpopulation, it was taken into account in the certainty of conclusions (see Section I 4.2).

Planned duration of follow-up observation

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

Table 8: Planned duration of follow-up observation – RCT, direct comparison: isatuximab + bortezomib + lenalidomide + dexamethasone[a] vs. bortezomib + lenalidomide + dexamethasone[b]

Study **Outcome category** **Outcome**	**Planned follow-up observation**
IMROZ	
Mortality	
Overall survival	Until death, lost to follow-up, or final data cut-off[c] (whichever occurred first)
Morbidity	
Symptoms (EORTC QLQ-C30, EORTC QLQ-MY20)	Up to a maximum of 90 ± 5 days after the last administration of the study medication
Health status (EQ-5D VAS)	
Health-related quality of life (EORTC C30, EORTC QLQ-MY20)	Up to a maximum of 90 ± 5 days after the last administration of the study medication
Side effects	
All outcomes in the side effects category	Up to a maximum of 30 days after the last administration of the study medication[d]

a. Followed by treatment with isatuximab + lenalidomide + dexamethasone in the maintenance phase (Cycle 5 and later).
b. Followed by treatment with lenalidomide + dexamethasone in the maintenance phase (Cycle 5 and later).
c. Planned for after approximately 202 deaths.
d. After the 30-day follow-up all ongoing treatment-related AEs and all SAEs (regardless of relationship with study treatment), and all new treatment-related AEs (regardless of severity), were followed up until resolution or stabilization.

AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

The observation periods for the outcomes of morbidity, health-related quality of life and side effects were systematically shortened because they were recorded only for the period of treatment with the study medication (plus 90 days for patient-relevant outcomes in the categories morbidity and health-related quality of life, and plus 30 days for side effects). However, to draw a reliable conclusion on the total study period or the time to patient death, it would also be necessary to record these outcomes for the total period, as was done for survival.

Characteristics of the relevant subpopulation

Table 9 shows the characteristics of the relevant subpopulation in the study included.

Table 9: Characteristics of the relevant subpopulation and study/treatment discontinuation – RCT, direct comparison: isatuximab + bortezomib + lenalidomide + dexamethasone[a] vs. bortezomib + lenalidomide + dexamethasone[b], relevant subpopulation (multipage table)

Study **Characteristic** **Category**	**Isatuximab + bortezomib + lenalidomide + dexamethasone[a]** **N = 196**	**Bortezomib + lenalidomide + dexamethasone[b]** **N = 136**
IMROZ		
Age [years], mean (SD)	73 (4)	73 (4)
< 65 years, n (%)	8 (4)	8 (6)
≥ 65 to < 70 years, n (%)	4 (2)[c]	3 (2)[c]
≥ 70 years, n (%)	184 (94)	125 (92)
Sex [F/M], %	46/54	46/54
Family origin, n (%)		
Caucasian	149 (76)	103 (76)
Asian	19 (10)	11 (8)
Other[d]	6 (3)[c]	4 (3)[c]
Not reported/missing	22 (11)	18 (13)
Geographical region, n (%)		
Europe	131 (67)	82 (60)
North America	2 (1)	5 (4)
Asia	19 (10)	9 (7)
Other countries	44 (22)	40 (30)
Time from initial diagnosis of multiple myeloma to randomization [months], mean (SD)	2.2 (4.2)	1.8 (3.3)
R-ISS stage at study entry[e], n (%)		
Stage I	41 (21)	24 (18)
Stage II	126 (64)	96 (71)
Stage III	24 (12)	12 (9)
Not classified	5 (3)	4 (3)
ECOG PS at baseline, n (%)		
0	91 (46)	54 (40)
1	75 (38)	63 (46)
2	29 (15)	19 (14)
3	1 (< 1)	0 (0)
Plasma cells in the bone marrow at study entry, n (%)		
> 0% – < 10%	8 (4)	2 (2)
≥ 10%	188 (96)[c]	134 (99)[c]
Bone marrow lesions (according to IRC) at study entry, n (%)	129 (72)[f]	95 (77)[f]
Prior surgery related to multiple myeloma	3 (2)	4 (3)
Prior radiotherapy related to multiple myeloma	7 (4)	7 (5)

Table 9: Characteristics of the relevant subpopulation and study/treatment discontinuation – RCT, direct comparison: isatuximab + bortezomib + lenalidomide + dexamethasone[a] vs. bortezomib + lenalidomide + dexamethasone[b], relevant subpopulation (multipage table)

Study Characteristic Category	Isatuximab + bortezomib + lenalidomide + dexamethasone[a] N = 196	Bortezomib + lenalidomide + dexamethasone[b] N = 136
Treatment discontinuation, n (%)[g]	ND	ND
Study discontinuation, n (%)[h]	ND	ND

a. Followed by treatment with isatuximab + lenalidomide + dexamethasone in the maintenance phase (Cycle 5 and later).
b. Followed by treatment with lenalidomide + dexamethasone in the maintenance phase (Cycle 5 and later).
c. Institute's calculation.
d. Includes Black or African American, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander.
e. Based on measurement of beta-2-microglobulin, albumin, serum LDH and FISH.
f. Data based on N = 179 vs. N = 123 patients of the relevant subpopulation.
g. Data only available for the total population [N = 265 vs. N = 181]. In the total population, treatment discontinuations occurred in 137 (52%) patients in the intervention arm and in 138 (76%) patients in the comparator arm. Common reasons for treatment discontinuation in the intervention versus the control arm were AE (23% vs. 28%), disease progression (14% vs. 37%) and patient decision (9% vs. 9%). An additional 1% vs. 0% of randomized patients in the total population never started treatment.
h. Data only available for the total population [N = 265 vs. N = 181]. In the total population, study discontinuations occurred in 87 (33%) patients in the intervention arm and in 72 (40%) patients in the comparator arm. Common reasons for study discontinuation in the intervention vs. control arm were patient decision (5% vs. 7%) and other (2% vs. 1%). The data additionally include patients who died during the course of the study (intervention arm: 26% vs. control arm: 33%).

ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; FISH: fluorescence in situ hybridization; IRC: independent review committee; LDH. lactate dehydrogenase; M: male; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; R-ISS: Revised International Staging System; SD: standard deviation

Overall, the patient characteristics for the relevant subpopulation were largely comparable between the 2 treatment arms. The patients' mean age was 73 years; and most patients were of Caucasian family origin (76%). In both study arms, the total proportion of men (54%) was slightly higher than the proportion of women (46%). The majority of patients included (85%) had an ECOG PS of 0 or 1 and were classified as R-ISS stage II (67%). At study entry, almost all patients (97%) had ≥ 10% of plasma cells in the bone marrow. In addition, 74% of the patients had bone marrow lesions at study entry.

Information on treatment and study discontinuations were only available for the total population of the IMROZ study. At the given data cut-off, there was a clear difference in treatment discontinuations between the study arms (52% versus 76%). This difference was due in particular to the higher proportion of disease progressions in the comparator arm (14% versus 37%).

Course of the study

Table 10 shows the patients' mean/median treatment duration and the mean/median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: isatuximab + bortezomib + lenalidomide + dexamethasone[a] vs. bortezomib + lenalidomide + dexamethasone[b], relevant subpopulation

Study **Duration of the study phase** **Outcome category/outcome**	**Isatuximab + bortezomib + lenalidomide + dexamethasone[a]** **N[c] = 196**	**Bortezomib + lenalidomide + dexamethasone[b]** **N[c] = 136**
IMROZ		
Treatment duration [months]		
Median [min; max]	50.6 [0.6; 68.8]	28.5 [0.6; 66.3]
Mean (SD)	40.3 (21.9)	31.5 (21.7)
Observation period [months]		
Overall survival[d]		
Median [Q1; Q3]	56.6 [38; 61.6]	55.9 [35.6; 60.7]
Mean (SD)	49 (18.7)	46.8 (19.9)
Morbidity (symptoms, health status), health-related quality of life		
EORTC QLQ-C30	N = 181	N = 127
Median [Q1; Q3]	52.3 [22.2; 58.6]	28.6 [11.5; 55]
Mean (SD)	41.5 (21.4)	32.2 (22.1)
EORTC QLQ-MY20	N = 181	N = 131
Median [Q1; Q3]	52.3 [22.8; 58.6]	28.6 [11.5; 55]
Mean (SD)	41.7 (21.3)	32.5 (22)
EQ-5D VAS	N = 179	N = 127
Median [Q1; Q3]	52.3 [22.2; 58.6]	28.6 [11.5; 55]
Mean (SD)	41.6 (21.4)	32.2 (22.1)
Side effects		
Median [Q1; Q3]	50.9 [19.3; 58.8]	29.1 [10.5; 55.1]
Mean (SD)	40.8 (21.9)	32.1 (21.6)

a. Followed by treatment with isatuximab + lenalidomide + dexamethasone in the maintenance phase (Cycle 5 and later).
b. Followed by treatment with lenalidomide + dexamethasone in the maintenance phase (Cycle 5 and later).
c. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
d. The observation periods between the date of randomization and the date of death or the date of censoring (last contact date or lost to follow-up or data cut-off for patients without event) are included in the calculation.

EORTC: European Organisation for Research and Treatment of Cancer; max: maximum; min: minimum; N: number of randomized patients; Q1: first quartile; Q3: third quartile; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Myeloma Module 20; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

For the relevant subpopulation, the median treatment duration in the IMROZ study was notably longer in the intervention arm (approx. 51 months) than in the comparator arm (approx. 29 months).

The median observation period for the outcome of overall survival was comparable between the treatment arms (57 versus 56 months). Since the observation periods for the outcomes in the categories of morbidity, health-related quality of life and side effects were linked to the treatment duration (see also Table 8), the median observation periods for these outcomes were notably longer in the intervention arm than in the comparator (approx. 52 vs. 29 months).

Subsequent therapies

There was no information on subsequent antineoplastic therapies for the relevant subpopulation. The data on subsequent antineoplastic therapies for the total population of the IMROZ study are therefore presented as an approximation in I Appendix B of the full dossier assessment and are assessed below.

In the total population, 52 (approx. 20%) of all patients enrolled in the intervention arm and 80 (approx. 44%) of all patients enrolled in the comparator arm had received at least one subsequent therapy at the first data cut-off. In relation to patients with disease progression according to the investigator (87 in the intervention arm; 96 in the comparator arm), approx. 60% of the patients in the intervention arm and approx. 83% of the patients in the comparator arm received subsequent therapy after disease progression.

As described above, patients with confirmed disease progression could switch from the comparator arm to treatment with isatuximab + lenalidomide + dexamethasone at the investigator's discretion during the maintenance phase if no other systemic cancer therapy had been administered and treatment with lenalidomide and dexamethasone had not been permanently discontinued. This applied to 25 out of 80 (31%) patients with subsequent therapy in the comparator arm. For these patients, however, it is not appropriate to add a CD38 antibody during ongoing treatment with a treatment regimen under which disease progression has already been determined (lenalidomide + dexamethasone; patients considered refractory to lenalidomide). In this treatment situation (refractoriness to lenalidomide), the German Society for Haematology and Medical Oncology (DGHO) recommends other drug combinations, such as the combination of daratumumab (CD38 antibody) with pomalidomide + dexamethasone, or daratumumab or isatuximab with carfilzomib + dexamethasone [17]. According to the DGHO recommendation, the treatment switching in the IMROZ study, from the comparator arm to the intervention arm after determined disease progression, therefore did not constitute adequate subsequent therapy. Furthermore, the study documents only contain information on subsequent therapies at drug

level aggregated across all lines of treatment (see Table 18 of the full dossier assessment). In principle, analyses of treatment regimens (drug combinations) in the individual lines of treatment, particularly for the relevant subpopulation, would be necessary for a final assessment of the subsequent therapies used.

Overall, the other treatments administered in the intervention and control arm (including CD38 antibodies, immunomodulators and proteasome inhibitors) reflect the diversity of treatment options in the therapeutic indication. However, in view of the existing uncertainties (no information on subsequent therapies in the relevant subpopulation, isatuximab administration with ongoing treatment with lenalidomide and dexamethasone after disease progression, and no information on the treatment regimens in the respective lines of treatment), it is not possible to conclusively assess whether the subsequent therapies used in the IMROZ study were adequate. As there was no statistically significant effect for the overall survival outcome (see Table 14), this did not have any consequences in the context of this benefit assessment.

Risk of bias across outcomes (study level)

Table 11 shows the risk of bias across outcomes (risk of bias at study level).

Table 11: Risk of bias across outcomes (study level) – RCT, direct comparison: isatuximab + bortezomib + lenalidomide + dexamethasone[a] vs. bortezomib + lenalidomide + dexamethasone[b]

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			
IMROZ	Yes	Yes	No	No	Yes	Yes	Low

a. Followed by treatment with isatuximab + lenalidomide + dexamethasone in the maintenance phase (Cycle 5 and later).
b. Followed by treatment with lenalidomide + dexamethasone in the maintenance phase (Cycle 5 and later).
RCT: randomized controlled trial

The risk of bias across outcomes was assessed as low for the IMROZ study.

Limitations resulting from the open-label study design are described in Section I 4.2 under outcome-specific risk of bias.

Transferability of the study results to the German health care context

According to the company, the IMROZ study was predominantly conducted in countries that belong to the Western world in terms of their social systems, culture and ethnicity. As examples, the company stated that 61.7% of the study participants came from Europe and 72.4% were of Caucasian family origin. Referencing the DGHO and the Robert Koch Institute (RKI), the company additionally described that the IMROZ study included a slightly higher proportion of male patients (53.1%) and that this concurred with real data in everyday practice, where the disease rate was slightly higher in men than women. The company concluded that the study population reflected the German health care context.

The company did not provide any further information on the transferability of the study results to the German health care context. However, the company's data referred to the total population of the IMROZ study. For the relevant subpopulation, the company did not provide any information on the transferability of the study results to the German health care context.

I 4 Results on added benefit

I 4.1 Outcomes included

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

- Mortality
  - Overall survival
- Morbidity
  - Symptoms, recorded using the EORTC QLQ-C30 and the EORTC QLQ-MY20
  - Health status, recorded using the EQ-5D visual analogue scale (VAS)
- Health-related quality of life
  - Recorded using the EORTC QLQ-C30 and the EORTC QLQ-MY20
- Side effects
  - SAEs
  - Severe AEs (CTCAE grade ≥ 3)
  - Discontinuation due to AEs
  - Infusion-related reactions
  - Peripheral neuropathy
  - Other specific AEs, if any

The patient-relevant outcomes selected deviate from those selected by the company, which used additional outcomes in its dossier (Module 4 C).

Table 12 shows for which outcomes data were available in the included study.

Table 12: Matrix of outcomes – RCT, direct comparison: isatuximab + bortezomib + lenalidomide + dexamethasone[a] vs. bortezomib + lenalidomide + dexamethasone[b]

Study	Outcomes									
	Overall survival	Symptoms (EORTC QLQ-C30, EORTC QLQ-MY20)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-MY20)	SAEs	Severe AEs[c]	Discontinuation due to AEs	Infusion-related reactions	Peripheral neuropathy	Further specific AEs[d]
IMROZ	Yes	Yes	Yes	Yes	Yes	Yes	No[e]	No[e]	No[f]	Yes

a. Followed by treatment with isatuximab + lenalidomide + dexamethasone in the maintenance phase (Cycle 5 and later).
b. Followed by treatment with lenalidomide + dexamethasone in the maintenance phase (Cycle 5 and later).
c. Severe AEs are operationalized as CTCAE grade ≥ 3.
d. The following events are considered (coded according to MedDRA): metabolism and nutrition disorders (SOC, severe AEs), respiratory, thoracic and mediastinal disorders (SOC, severe AEs).
e. No suitable data; for justification, see next Section and Section I 4.2 of this dossier assessment.
f. No data available for the relevant subpopulation.

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

Notes on outcomes

Outcomes in the categories morbidity and health-related quality of life

In Module 4 C, the company presented responder analyses for the patient-reported outcomes on morbidity and health-related quality of life measured using the EORTC QLQ-C30 and the additional module EORCT QLQ-MY20, in each case for time to first deterioration and time to permanent deterioration by ≥ 10 points (respective scale range 0 to 100); and for the outcome health status measured using the EQ-5D VAS responder analyses for first and permanent deterioration by ≥ 15 points (respective scale range 0 to 100). The operationalization of time to first deterioration was prespecified. The analysis for the time to permanent deterioration was prepared post hoc for the dossier. In Module 4 C, the company used the results of the responder analyses on permanent deterioration as the primary analysis. In addition, the

company considered the results of the responder analyses on the first deterioration in the derivation of the added benefit.

In the given data situation, in which the observation periods of all patient-reported outcomes differed notably between the study arms (see Table 10), this benefit assessment used the analyses of the time to first deterioration – as described by the G-BA [18]. The analyses presented by the company for the time to permanent deterioration are therefore not commented on further.

Outcomes in the category of side effects

Discontinuation due to AEs

For the outcome discontinuation due to AEs, only analyses of the time to discontinuation of all drug components were available in Module 4 C. Analyses for discontinuation of at least one drug component were missing. Patients in the IMROZ study could continue treatment with the remaining drug components after discontinuing one drug component. An analysis on the discontinuation of all drug components alone could not be meaningfully interpreted in the present data situation (up to 4 drug components in the intervention arm and up to 3 drug components in the comparator arm). Regardless of this, analyses on the discontinuation of at least one drug component are preferable, as any AE leading to discontinuation of any treatment component is relevant. Consequently, results for the analysis of the time to discontinuation of at least one drug component were required for the benefit assessment.

Infusion-related reactions

Due to the open-label study design of the IMROZ study (without placebo infusion) and regular intravenous administration of isatuximab (and dexamethasone) in the intervention arm (see Table 7), infusion-related reactions could generally only be recorded in the intervention arm. According to the statistical analysis plan of the IMROZ study, whenever possible, only the clinical diagnosis using the respective Preferred Terms (PTs) (e.g. infusion-related reaction) was to be recorded as AE instead of the underlying individual symptoms. However, the underlying symptoms were recorded in a separate documentation form (case report form [CRF]) and were therefore generally available.

In order to obtain informative data on the outcome infusion-related reactions for the benefit assessment in unblinded studies comparing oral and intravenous drugs, it would first be necessary for the individual symptoms underlying the infusion-related reactions to be included in the general analysis of AEs. For this to be possible, the respective symptoms have to be included in the AE analyses via the corresponding PT (e.g. the PT chills) (as was the case in the MAIA study, for example, see [19]). As the underlying symptoms of the infusion-related reactions in the IMROZ study were documented in a separate CRF as described above, it would in principle be possible to include them in the general analyses of AEs. Based on this, an

aggregated analysis of all symptomatic AEs potentially relevant to the infusion-related reactions (e.g. chills, nausea and vomiting, regardless of whether or not they are temporally related to an infusion) is necessary. Specific AEs that represent an infusion-related reaction should either be predefined or refer to content-based compilations based on publications or compilations of the Medical Dictionary for Regulatory Activities (MedDRA) system (e.g. a PT list) and be recorded in both study arms. In Module 4 C, however, the company only presented analyses for the PT infusion-related reaction and for the predefined AE of special interest (AESI) infusion reaction with CTCAE grade ≥ 3. These analyses are not suitable for the benefit assessment, as the respective events could only be recorded in the intervention arm. Although 2 events for the PT infusion-related reaction (AE) were recorded in the comparator arm in the given data cut (see Table 19 of the full dossier assessment), it is unclear whether these were due to subsequent therapy (e.g. as part of the switch from the comparator arm to the intervention arm, see Section I 3.2). Hence no suitable data were available for the outcome infusion-related reactions.

The company's approach (underlying symptoms of infusion-related reactions were not included in the analyses of side effects for the intervention arm) made it difficult to interpret the results for all System Organ Classes (SOCs)/PTs that frequently occurred in relation to infusions (e.g. vomiting, respiratory, thoracic and mediastinal disorders, skin and subcutaneous tissue disorders). This was not relevant for the SOCs/PTs for severe AEs (CTCAE grade ≥ 3) and SAEs, as only 6 severe symptom events (CTCAE grade ≥ 3) were recorded in the total population (no data available for SAEs). However, it was unclear for the non-serious/non-severe AEs whether the effect estimate would change for the individual PTs when considering all events that occurred during the course of the study (regardless of whether they were infusion-related or not) at the PT and SOC level. It can therefore not be ruled out with sufficient certainty that potential disadvantages in individual SOCs or PTs were overlooked.

Peripheral neuropathy

In the therapeutic indication in question, peripheral neuropathy events are relevant AEs during treatment with bortezomib. In the statistical analysis plan, the company prespecified peripheral neuropathies as "other significant AEs" and recorded them as peripheral neuropathy using the Standardized MedDRA Query (SMQ, narrow). For this outcome, only analyses of event rates including severity classification according to CTCAE grade ≥ 3 for the total population were available. The operationalization of severe peripheral neuropathy (CTCAE grade ≥ 3) was relevant, but no analyses were available for the relevant subpopulation.

I 4.2 Risk of bias

Table 13 describes the risk of bias for the results of the relevant outcomes.

Table 13: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: isatuximab + bortezomib + lenalidomide + dexamethasone[a] vs. bortezomib + lenalidomide + dexamethasone[b]

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

a. Followed by treatment with isatuximab + lenalidomide + dexamethasone in the maintenance phase (Cycle 5 and later).
b. Followed by treatment with lenalidomide + dexamethasone in the maintenance phase (Cycle 5 and later).
c. Severe AEs are operationalized as CTCAE grade ≥ 3.
d. The following events are considered (coded according to MedDRA): metabolism and nutrition disorders (SOC, severe AEs), respiratory, thoracic and mediastinal disorders (SOC, severe AEs).
e. Lack of blinding in subjective recording of outcomes.
f. Incomplete observations for potentially informative reasons with different follow-up observations.
g. No suitable data; for justification, see Section I 4.1 and next Section).
h. No data available for the relevant subpopulation.
i. Incomplete consideration of the symptoms underlying the infusion-related reactions in the analyses of non-severe/non-serious AEs (see Section I 4.1 and next Section).

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

The risk of bias of the result on the outcome of overall survival was rated as low.

For the outcomes on symptoms (recorded using the EORTC QLQ-C30 and the EORTC QLQ-MY20), health status (recorded using the EQ-5D VAS) and on health-related quality of life (recorded using the EORTC QLQ-C30 and the EORTC QLQ-MY20), the risk of bias of the results was rated as high due to the lack of blinding in subjective recording of outcomes. In addition, the risk of bias of the results of these patient-reported outcomes and the outcomes in the side effects category (SAEs, severe AEs and the specific AEs metabolism and nutrition disorders [SOC, severe AEs] and respiratory, thoracic and mediastinal disorders [SOC, severe AEs]) was rated as high due to incomplete observations for potentially informative reasons in the presence of different follow-up observations between the treatment groups. Other non-severe/non-serious specific AEs are not shown, as there were no statistically significant

differences in each case based on the frequencies. As the symptoms underlying the infusion-related reactions in the intervention arm were not included in the analyses of AEs, further potential disadvantages of non-severe/non-serious specific AEs may be overlooked, contributing to the high risk of bias of the results.

It should also be noted that in the comparator arm there were relevant deviations in the determination of progression by the investigators and the IRC. The investigators commonly determined progression that was not confirmed by the IRC. Since treatment discontinuation (and thus the discontinuation of observation for further outcomes, see Table 8) was based on the investigator assessment, the observation of further outcomes was potentially discontinued even earlier than planned, which contributed to the high risk of bias.

No (suitable) analyses were available for the outcomes discontinuation due to AEs, infusion-related reactions and peripheral neuropathy (see Section I 4.1). The risk of bias for these outcomes was therefore not assessed.

Summary assessment of the certainty of conclusions

Irrespective of the aspects described under the risk of bias, the certainty of conclusions of the study results was in principle limited due to the uncertainties described in Section I 3.2 regarding ASCT ineligibility of the relevant subpopulation included. The IMROZ study can therefore at most be used to derive hints, for example of an added benefit.

I 4.3 Results

Table 14 summarizes the results of the comparison of isatuximab + bortezomib + lenalidomide + dexamethasone with bortezomib + lenalidomide + dexamethasone in patients with newly diagnosed multiple myeloma who are ineligible for ASCT. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

The Kaplan-Meier curves on the time-to-event analyses are presented in I Appendix C of the full dossier assessment, and the tables on common AEs, SAEs and severe AEs in I Appendix D of the full dossier assessment.

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: isatuximab + bortezomib + lenalidomide + dexamethasone[a] vs. bortezomib + lenalidomide + dexamethasone[b], relevant subpopulation (multipage table)

Study Outcome category Outcome	Isatuximab + bortezomib + lenalidomide + dexamethasone[a]		Bortezomib + lenalidomide + dexamethasone[b]		Isatuximab + bortezomib + lenalidomide + dexamethasone[a] vs. bortezomib + lenalidomide + dexamethasone[b]
	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[c]
IMROZ					
Mortality					
Overall survival	196	NA 57 (29.1)	136	NA [63.6; NC] 48 (35.3)	0.80 [0.55; 1.18]; 0.256
Morbidity					
Symptoms (EORTC QLQ-C30 – time to first deterioration[d])					
Fatigue	196	2.9 [2.8; 4.2] 143 (73.0)	136	2.8 [1.6; 2.9] 106 (77.9)	0.81 [0.63; 1.04]; 0.112
Nausea and vomiting	196	18.2 [12.4; 31.0] 106 (54.1)	136	8.5 [6.8; 12.7] 78 (57.4)	0.72 [0.54; 0.97]; 0.031
Pain	196	6.1 [4.4; 8.4] 125 (63.8)	136	4.4 [2.9; 6.0] 91 (66.9)	0.79 [0.60; 1.04]; 0.089
Dyspnoea	196	11.2 [7.0; 16.3] 114 (58.2)	136	3.6 [2.9; 6.6] 91 (66.9)	0.61 [0.46; 0.80]; < 0.001
Insomnia	196	4.3 [2.9; 6.9] 122 (62.2)	136	2.9 [2.8; 4.3] 86 (63.2)	0.84 [0.64; 1.12]; 0.239
Appetite loss	196	7.4 [5.8; 9.7] 119 (60.7)	136	5.7 [4.2; 7.0] 93 (68.4)	0.75 [0.57; 0.99]; 0.046
Constipation	196	5.6 [3.1; 10.7] 114 (58.2)	136	3.2 [2.6; 5.6] 81 (59.6)	0.87 [0.66; 1.16]; 0.365
Diarrhoea	196	9.0 [6.8; 13.6] 132 (67.3)	136	5.8 [4.5; 7.6] 95 (69.9)	0.77 [0.59; 1.00]; 0.051
Symptoms (EORTC QLQ-MY20 – time to first deterioration[d])					
Disease symptoms	196	11.4 [7.4; 20.4] 111 (56.6)	136	12.2 [6.1; 25.1] 76 (55.9)	1.05 [0.78; 1.40]; 0.765
Side effects	196	4.5 [4.1; 6.9] 128 (65.3)	135	4.2 [2.9; 6.1] 95 (70.4)	0.82 [0.62; 1.07]; 0.137
Health status (EQ-5D VAS – time to first deterioration[e])	196	17.0 [8.5; 38.2] 97 (49.5)	136	7.1 [4.7; 27.3] 75 (55.1)	0.78 [0.57; 1.05]; 0.104

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: isatuximab + bortezomib + lenalidomide + dexamethasone[a] vs. bortezomib + lenalidomide + dexamethasone[b], relevant subpopulation (multipage table)

Study Outcome category Outcome	Isatuximab + bortezomib + lenalidomide + dexamethasone[a]		Bortezomib + lenalidomide + dexamethasone[b]		Isatuximab + bortezomib + lenalidomide + dexamethasone[a] vs. bortezomib + lenalidomide + dexamethasone[b]
	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[c]
Health-related quality of life					
EORTC QLQ-C30 – time to first deterioration[f]					
Global health status	196	6.6 [4.2; 11.1] 119 (60.7)	136	4.2 [2.9; 5.8] 88 (64.7)	0.79 [0.60; 1.05]; 0.106
Physical functioning	196	5.6 [4.2; 6.9] 123 (62.8)	136	4.3 [2.9; 5.7] 94 (69.1)	0.77 [0.59; 1.02]; 0.069
Role functioning	196	4.4 [3.0; 6.1] 126 (64.3)	136	2.9 [1.7; 4.3] 93 (68.4)	0.76 [0.58; 0.99]; 0.048
Emotional functioning	196	9.5 [7.1; 19.5] 113 (57.7)	136	7.5 [4.3; 23.4] 75 (55.1)	0.90 [0.67; 1.21]; 0.488
Cognitive functioning	196	5.8 [4.2; 8.4] 138 (70.4)	136	4.5 [2.9; 6.8] 100 (73.5)	0.80 [0.61; 1.04]; 0.09
Social functioning	196	4.2 [2.8; 4.4] 142 (72.4)	136	2.8 [2.8; 3.0] 96 (70.6)	0.85 [0.65; 1.11]; 0.245
EORTC QLQ-MY20 – time to first deterioration[f]					
Future perspective	196	7.9 [5.7; 18.5] 110 (56.1)	136	3.3 [2.9; 6.6] 87 (64.0)	0.74 [0.56; 0.99]; 0.046
Body image	196	6.6 [4.3; 17.2] 118 (60.2)	136	4.3 [3.3; 9.3] 92 (67.6)	0.81 [0.61; 1.06]; 0.126
Side effects[g]					
AEs (supplementary information)	195	0.2 [0.1; 0.3] 194 (99.5)	136	0.2 [0.1; 0.3] 134 (98.5)	-
SAEs	195	12.2 [8.4; 24.3] 139 (71.3)	136	5.3 [2.5; 11.6] 100 (73.5)	0.79 [0.61; 1.03]; 0.078[h]
Severe AEs[i]	195	2.0 [1.4; 2.9] 176 (90.3)	136	1.5 [0.9; 2.3] 117 (86.0)	0.95 [0.75; 1.20]; 0.685[h]
Discontinuation due to AEs	No suitable data[j]				
Infusion-related reactions	No suitable data[j]				
Peripheral neuropathy	No suitable data[k]				

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: isatuximab + bortezomib + lenalidomide + dexamethasone[a] vs. bortezomib + lenalidomide + dexamethasone[b], relevant subpopulation (multipage table)

Study Outcome category Outcome	Isatuximab + bortezomib + lenalidomide + dexamethasone[a]		Bortezomib + lenalidomide + dexamethasone[b]		Isatuximab + bortezomib + lenalidomide + dexamethasone[a] vs. bortezomib + lenalidomide + dexamethasone[b]
	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[c]
Metabolism and nutrition disorders (SOC, severe AEs[i])	195	NA 13 (6.7)	136	NA [62.2; NC] 22 (16.2)	0.36 [0.18; 0.71]; 0.002[h]
Respiratory, thoracic and mediastinal disorders (SOC, severe AEs[i])	195	NA 15 (7.7)	136	NA 20 (14.7)	0.45 [0.23; 0.89]; 0.018[h]

a. Followed by treatment with isatuximab + lenalidomide + dexamethasone in the maintenance phase (Cycle 5 and later).
b. Followed by treatment with lenalidomide + dexamethasone in the maintenance phase (Cycle 5 and later).
c. Effect, CI and p-value: Cox proportional hazards model and log-rank test; each stratified by age (< 70 years; ≥ 70 years) and R-ISS stage (I or II; III or not classified)
d. An increase in EORTC QLQ-C30 and EORTC QLQ-MY20 by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
e. An EQ-5D VAS score decrease by ≥ 15 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
f. A decrease in EORTC QLQ-C30 and EORTC QLQ-MY20 by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
g. Excluding the PTs malignant neoplasm progression, bone metastases, plasma cell leukaemia and plasma cell myeloma.
h. Effect, CI and p-value: Cox proportional hazards model and log-rank test; each unstratified.
i. Operationalized as CTCAE grade ≥ 3.
j. See Sections I 4.1 and I 4.2 of this dossier assessment for the reasoning.
k. No data for the relevant subpopulation.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Myeloma Module 20; R-ISS: Revised International Staging System; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Based on the available information, at most hints, for example of an added benefit, can be determined for all outcomes (see Sections I 3.2 and I 4.2 for the reasoning).

Mortality

Overall survival

There was no statistically significant difference between the treatment arms for the outcome overall survival. There was no hint of an added benefit of isatuximab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone; an added benefit is therefore not proven.

Morbidity

Symptoms (EORTC QLQ-C30)

Dyspnoea

A statistically significant difference in favour of isatuximab + bortezomib + lenalidomide + dexamethasone was shown for the outcome dyspnoea. There is a hint of an added benefit of isatuximab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone.

Nausea and vomiting, appetite loss

A statistically significant difference in favour of isatuximab + bortezomib + lenalidomide + dexamethasone was shown for the outcomes nausea and vomiting, and appetite loss. However, the difference was no more than marginal for these outcomes in the category of non-serious/non-severe symptoms/late complications. In either case, there was no hint of an added benefit of isatuximab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone; an added benefit is therefore not proven for either outcome.

Fatigue, pain, insomnia, constipation and diarrhoea

No statistically significant difference between the treatment arms was shown for any of the outcomes fatigue, pain, insomnia, constipation and diarrhoea. In either case, there was no hint of an added benefit of isatuximab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone; an added benefit is therefore not proven for either outcome.

EORTC QLQ-MY20

Disease symptoms and side effects

There was no statistically significant difference between the treatment arms for either of the outcomes disease symptoms and side effects. In either case, there was no hint of an added benefit of isatuximab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone; an added benefit is therefore not proven for either outcome.

Health status (EQ-5D VAS)

No statistically significant difference between the treatment arms was shown for the outcome health status, recorded using the EQ-5D VAS. There was no hint of an added benefit of isatuximab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

Role functioning

A statistically significant difference in favour of isatuximab + bortezomib + lenalidomide + dexamethasone was shown for the outcome role functioning. There is a hint of an added benefit of isatuximab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone.

Global health status, physical functioning, emotional functioning, cognitive functioning and social functioning

No statistically significant difference between the treatment arms was shown for any of the outcomes global health status, physical functioning, emotional functioning, cognitive functioning and social functioning. In each case, there was no hint of an added benefit of isatuximab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone; an added benefit is therefore not proven for these outcomes.

EORTC QLQ-MY20

Future perspective

A statistically significant difference in favour of isatuximab + bortezomib + lenalidomide + dexamethasone was shown for the outcome future perspective. There is a hint of an added benefit of isatuximab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone.

Body image

No statistically significant difference between the treatment arms was shown for the outcome body image. There was no hint of an added benefit of isatuximab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone; an added benefit is therefore not proven.

Side effects

SAEs and severe AEs

There was no statistically significant difference between the treatment arms for the outcomes of SAEs and severe AEs. In either case, there was no hint of greater or lesser harm from

isatuximab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone; greater or lesser harm is therefore not proven for either of the outcomes.

Discontinuation due to AEs and infusion-related reactions

The analyses presented by the company for the outcomes discontinuation due to AEs and infusion-related reactions were not suitable for the benefit assessment (see Section I 4.1). In either case, there was no hint of greater or lesser harm from isatuximab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone; greater or lesser harm is therefore not proven for either of the outcomes.

Peripheral neuropathy

No analyses for the relevant subpopulation were available for the outcome peripheral neuropathy (see Section I 4.1). There was no hint of greater or lesser harm from isatuximab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone; greater or lesser harm is therefore not proven.

Metabolism and nutrition disorders (SOC, severe AEs) and respiratory, thoracic and mediastinal disorders (SOC, severe AEs)

For each of the outcomes metabolism and nutrition disorders (SOC, severe AEs) and respiratory, thoracic and mediastinal disorders (SOC, severe AEs), there was a statistically significant difference to the advantage of isatuximab + bortezomib + lenalidomide + dexamethasone. There was a hint of lesser harm of isatuximab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone.

I 4.4 Subgroups and other effect modifiers

No subgroup analyses for the IMROZ study were used as part of the benefit assessment. The reasons for this are as follows:

The IMROZ study was relevant for the given research question. However, with regard to the relevant subpopulation included (patients ineligible for ASCT), the results were subject to uncertainty (see Section I 3.2). For downstream subgroup analyses, this resulted in the following additional uncertainty: It is unknown how patients who were still eligible for ASCT were distributed across possible subgroups and to what extent this would lead to a bias in the subgroup results. The results from the subgroup analyses were therefore assessed as non-interpretable, and no subgroup analyses were used for this benefit assessment.

I 5 Probability and extent of added benefit

The probability and extent of 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 IQWiG *General Methods* [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.

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Chapter I 4 (see Table 15).

Determination of the outcome category for symptom outcomes

For the symptom outcomes below, it could not be inferred from the dossier whether they are serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Symptoms

For the symptom outcomes (nausea and vomiting, dyspnoea and appetite loss, recorded using the EORTC QLQ-C30), insufficient severity data were available which would allow a classification as serious/severe. The symptom outcomes were therefore assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Table 15: Extent of added benefit at outcome level: Isatuximab + bortezomib + lenalidomide + dexamethasone[a] vs. bortezomib + lenalidomide + dexamethasone[b] (multipage table)

Outcome category **Outcome**	**Isatuximab + bortezomib + lenalidomide + dexamethasone[a] vs. bortezomib + lenalidomide + dexamethasone[b]** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[c]**	**Derivation of extent[d]**
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	NA vs. NA 0.80 [0.55; 1.18]; p = 0.256	Lesser benefit/added benefit not proven
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30 – time to first deterioration by ≥ 10 points)		
Fatigue	2.9 vs. 2.8 0.81 [0.63; 1.04]; p = 0.112	Lesser benefit/added benefit not proven
Nausea and vomiting	18.2 vs. 8.5 0.72 [0.54; 0.97]; p = 0.031	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Lesser benefit/added benefit not proven[e]
Pain	6.1 vs. 4.4 0.79 [0.60; 1.04]; p = 0.089	Lesser benefit/added benefit not proven
Dyspnoea	11.2 vs. 3.6 0.61 [0.46; 0.80]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ Added benefit, extent: minor
Insomnia	4.3 vs. 2.9 0.84 [0.64; 1.12]; p = 0.239	Lesser benefit/added benefit not proven
Appetite loss	7.4 vs. 5.7 0.75 [0.57; 0.99]; p = 0.046	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Lesser benefit/added benefit not proven[e]
Constipation	5.6 vs. 3.2 0.87 [0.66; 1.16]; p = 0.365	Lesser benefit/added benefit not proven

Table 15: Extent of added benefit at outcome level: Isatuximab + bortezomib + lenalidomide + dexamethasone[a] vs. bortezomib + lenalidomide + dexamethasone[b] (multipage table)

Outcome category **Outcome**	**Isatuximab + bortezomib + lenalidomide + dexamethasone[a] vs. bortezomib + lenalidomide + dexamethasone[b]** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[c]**	**Derivation of extent[d]**
Diarrhoea	9.0 vs. 5.8 0.77 [0.59; 1.00]; p = 0.051	Lesser benefit/added benefit not proven
Symptoms (EORTC QLQ-MY20 – time to first deterioration by ≥ 10 points)		
Disease symptoms	11.4 vs. 12.2 1.05 [0.78; 1.40]; p = 0.765	Lesser benefit/added benefit not proven
Side effects	4.5 vs. 4.2 0.82 [0.62; 1.07]; p = 0.137	Lesser benefit/added benefit not proven
Health status (time to first deterioration by ≥ 15 points)		
EQ-5D VAS	17.0 vs. 7.1 0.78 [0.57; 1.05]; p = 0.104	Lesser benefit/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 (time to first deterioration by ≥ 10 points)		
Global health status	6.6 vs. 4.2 0.79 [0.60; 1.05]; p = 0.106	Lesser benefit/added benefit not proven
Physical functioning	5.6 vs. 4.3 0.77 [0.59; 1.02]; p = 0.069	Lesser benefit/added benefit not proven
Role functioning	4.4 vs. 2.9 0.76 [0.58; 0.99]; p = 0.048 Probability: hint	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Added benefit, extent: minor
Emotional functioning	9.5 vs. 7.5 0.90 [0.67; 1.21]; p = 0.488	Lesser benefit/added benefit not proven
Cognitive functioning	5.8 vs. 4.5 0.80 [0.61; 1.04]; p = 0.09	Lesser benefit/added benefit not proven

Table 15: Extent of added benefit at outcome level: Isatuximab + bortezomib + lenalidomide + dexamethasone[a] vs. bortezomib + lenalidomide + dexamethasone[b] (multipage table)

Outcome category **Outcome**	**Isatuximab + bortezomib + lenalidomide + dexamethasone[a] vs. bortezomib + lenalidomide + dexamethasone[b]** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[c]**	**Derivation of extent[d]**
Social functioning	4.2 vs. 2.8 0.85 [0.65; 1.11]; p = 0.245	Lesser benefit/added benefit not proven
EORTC QLQ-MY20 (time to first deterioration)		
Future perspective	7.9 vs. 3.3 0.74 [0.56; 0.99]; p = 0.046 Probability: hint	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Added benefit, extent: minor
Body image	6.6 vs. 4.3 0.81 [0.61; 1.06]; p = 0.126	Lesser benefit/added benefit not proven
Side effects		
SAEs	12.2 vs. 5.3 0.79 [0.61; 1.03]; p = 0.078	Greater/lesser harm not proven
Severe AEs	2.0 vs. 1.5 0.95 [0.75; 1.20]; p = 0.685	Greater/lesser harm not proven
Discontinuation due to AEs	No suitable data	Greater/lesser harm not proven
Infusion-related reactions	No suitable data	Greater/lesser harm not proven
Peripheral neuropathy	No suitable data	Greater/lesser harm not proven
Metabolism and nutrition disorders (SOC, severe AEs)	NA vs. NA 0.36 [0.18; 0.71]; p = 0.002 Probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Added benefit, extent: major
Respiratory, thoracic and mediastinal disorders (SOC, severe AEs)	NA vs. NA 0.45 [0.23; 0.89]; p = 0.018 Probability: hint	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Added benefit, extent: considerable

Table 15: Extent of added benefit at outcome level: Isatuximab + bortezomib + lenalidomide + dexamethasone[a] vs. bortezomib + lenalidomide + dexamethasone[b] (multipage table)

Outcome category **Outcome**	**Isatuximab + bortezomib + lenalidomide + dexamethasone[a] vs. bortezomib + lenalidomide + dexamethasone[b]** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[c]**	**Derivation of extent[d]**
a. Followed by treatment with isatuximab + lenalidomide + dexamethasone in the maintenance phase (Cycle 5 and later). b. Followed by treatment with lenalidomide + dexamethasone in the maintenance phase (Cycle 5 and later). c. Probability provided if there is a statistically significant and relevant effect. d. Estimates of the effect size are made with different limits depending on the outcome category using the upper limit of the confidence interval (CI_u). e. The extent of the effect in this non-serious/non-severe outcome was no more than marginal. AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; NA: not achieved; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Myeloma Module 20; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale		

I 5.2 Overall conclusion on added benefit

Table 16 summarizes the results taken into account for the overall conclusion on the extent of added benefit.

Table 16: Positive and negative effects from the assessment of isatuximab + bortezomib + lenalidomide + dexamethasone[a] in comparison with bortezomib + lenalidomide + dexamethasone[b]

Positive effects	Negative effects
Outcomes with observation over the entire study duration	
-	-
Outcomes with shortened observation period	
Non-serious/non-severe symptoms/late complications ▪ Dyspnoea: hint of an added benefit – extent: minor	-
Health-related quality of life ▪ Role functioning: hint of an added benefit – extent: minor ▪ Future perspective: hint of an added benefit – extent minor	-
Serious/severe side effects ▪ Severe AEs: ▫ Metabolism and nutrition disorders: hint of an added benefit – extent: major ▫ Respiratory, thoracic and mediastinal disorders: hint of an added benefit – extent: considerable	-
No (suitable) data are available for the following outcomes in the outcome category of side effects: discontinuation due to AEs, infusion-related reactions, peripheral neuropathy	
a. Followed by treatment with isatuximab + lenalidomide + dexamethasone in the maintenance phase (Cycle 5 and later). b. Followed by treatment with lenalidomide + dexamethasone in the maintenance phase (Cycle 5 and later). AE: adverse event	

Overall, only positive effects of varying extent were shown for isatuximab + bortezomib + lenalidomide + dexamethasone.

For each of the patient-reported outcomes on symptoms (dyspnoea) and health-related quality of life (role functioning and future perspective), there was a hint of an added benefit of minor extent. In addition, for 2 specific AEs in the category of serious/severe side effects, there was a hint of lesser harm of considerable or major extent. However, no suitable data were available for the outcome discontinuation due to AEs, infusion-related reactions and for the outcome peripheral neuropathy. Furthermore, the symptoms underlying the infusion-related reactions were not included in the analyses of AEs, so that further disadvantages in the specific AEs were potentially overlooked.

In summary, there was a hint of minor added benefit of isatuximab + bortezomib + lenalidomide + dexamethasone versus bortezomib + lenalidomide + dexamethasone for patients with newly diagnosed multiple myeloma who are ineligible for ASCT.

Table 17 summarizes the result of the assessment of the added benefit of isatuximab + bortezomib + lenalidomide + dexamethasone in comparison with the ACT.

Table 17: Isatuximab + bortezomib + lenalidomide + dexamethasone – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant	▪ daratumumab in combination with lenalidomide and dexamethasone, or ▪ daratumumab in combination with bortezomib, melphalan and prednisone, or ▪ bortezomib in combination with melphalan and prednisone, or ▪ bortezomib in combination with lenalidomide and dexamethasone, or ▪ thalidomide in combination with melphalan and prednisone, or ▪ bortezomib in combination with cyclophosphamide and dexamethasone (only for patients with peripheral polyneuropathy or an increased risk of developing peripheral polyneuropathy[b])	Hint of minor added benefit[c]

a. Presented is the ACT specified by the G-BA.
b. See Appendix VI to Section K of the Pharmaceutical Directive.
c. Only patients with an ECOG PS of 0 to 2 were included in the IMROZ study. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of > 2.

ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee

The assessment described above deviates from that of the company, which derived an indication of considerable added benefit based on the results of the total population of the IMROZ study.

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

I 6 References for English extract

Please see full dossier assessment for full reference list.

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The full report (German version) is published under https://www.iqwig.de/en/projects/a25-20.html.