IQWiG Reports – Commission No. A21-61

Isatuximab (multiple myeloma after ≥ 2 prior therapies) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Isatuximab (multiples Myelom nach* ≥ 2 Vortherapien*) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 12 August 2021). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Isatuximab (multiple myeloma after ≥ 2 prior therapies) – Benefit assessment according to §35a Social Code Book V

Commissioning agency
Federal Joint Committee

Commission awarded on
12 May 2021

Internal Commission No.
A21-61

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

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Keywords: Isatuximab, Pomalidomide, Dexamethasone, Multiple Myelom, Benefit Assessment, NCT02990338

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AESI	Adverse Event of Special Interest
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European Public Assessment Report;
FDA	Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
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-Multiple Myeloma 20
RCT	randomized controlled trial
R-ISS	Revised International Staging System
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
TEAE	Treatment-Emergent Adverse Event

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug isatuximab in combination with pomalidomide and dexamethasone (isatuximab + pomalidomide + dexamethasone). The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 12 May 2021.

Research question

The aim of the present report is the assessment of the added benefit of isatuximab + pomalidomide + dexamethasone compared with the appropriate comparator therapy (ACT) in patients with relapsed and refractory multiple myeloma who have received ≥ 2 prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression under the last therapy.

The ACT specified by the G-BA is shown in Table 2.

Table 2: Research question of the benefit assessment of isatuximab + pomalidomide + dexamethasone

Therapeutic indication	ACT[a]
Adult patients with relapsed and refractory multiple myeloma who have received ≥ 2 prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression under the last therapy[b]	▪ Bortezomib in combination with dexamethasone, or ▪ lenalidomide in combination with dexamethasone, or ▪ **pomalidomide in combination with dexamethasone**, or ▪ elotuzumab in combination with lenalidomide and dexamethasone, or ▪ elotuzumab in combination with pomalidomide and dexamethasone, or ▪ carfilzomib in combination with lenalidomide and dexamethasone, or ▪ carfilzomib in combination with dexamethasone, or ▪ daratumumab in combination with lenalidomide and dexamethasone, or ▪ daratumumab in combination with bortezomib and dexamethasone
a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b. It is assumed that high-dose chemotherapy with stem cell transplantation is not an option for the patients at the time point of their current treatment. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA's specification of the ACT and did not limit its information retrieval to one of the options listed in Table 2; in Module 4 A, the company provides evidence of the added benefit of pomalidomide in combination with dexamethasone.

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

Study pool and study design

The study ICARIA-MM was used for the benefit assessment. ICARIA-MM is an ongoing RCT that compares isatuximab + pomalidomide + dexamethasone with pomalidomide + dexamethasone. The study investigates adults with refractory or relapsed and refractory multiple myeloma who have received at least 2 prior therapies including lenalidomide and a proteasome inhibitor. They had to have relapsed after treatment with lenalidomide or a proteasome inhibitor or had to be refractory to the treatment or had to have developed intolerable toxicity. Moreover, patients had to show progression of the disease under the last therapy. This progression had to have occurred during the last therapy or within 60 days of the end of the last therapy before study entry, i.e. refractory to the last line of treatment.

The therapeutic indication specified in the approval, i.e. relapsed and refractory multiple myeloma, is represented in the ICARIA-MM study. Based on the therapeutic algorithm in the guidelines, it is assumed that high-dose chemotherapy with subsequent stem cell transplantation was not indicated for patients without previous stem cell transplantation in the present therapeutic indication.

307 patients were randomly assigned either to treatment with isatuximab + pomalidomide + dexamethasone (154 patients) or to treatment with pomalidomide + dexamethasone (153 patients). Stratification factors were age (< 75 years vs. ≥ 75 years) and number of prior therapies (2 or 3 vs. ≥ 4 lines of treatment). Neither patients nor study staff are blinded to the treatment. With slight deviations (administration volume and premedication), the study treatment corresponds to the information in the respective Summary of Product Characteristics (SPC).

Primary outcome is progression-free survival (PFS); overall survival, symptoms, health status and adverse events (AEs) are recorded as patient-relevant secondary outcomes.

Two data cut-offs are available for the study. The first data cut-off of 11 October 2018/22 November 2018 is a planned data cut-off for PFS to obtain the approval with analyses on all outcomes. The second data cut-off of 1 October 2020 was subsequently planned for overall survival and includes analyses on overall survival and the outcomes on side effects. In the present benefit assessment, the results of the first data cut-off were used for the outcomes on morbidity, symptoms and health-related quality of life; the results of the second data cut-off were used for overall survival and the outcomes on side effects.

Risk of bias and certainty of conclusions

The results for all relevant outcomes except overall survival have a high risk of bias. The reasons vary depending on the outcome:

On the one hand, the results for the outcomes on morbidity, symptoms and health-related quality of life have a high risk of bias due to the open-label study design, since the recording of the questionnaires is based on the subjective assessment of the patients. On the other hand, the response rates differ between the study arms and show a clear decrease in the course of the study.

Due to potentially informative censoring, the risk of bias of the results for the outcomes "serious adverse events (SAEs)" and "severe adverse events (severe AEs)" (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)" was rated as high.

Therefore, an indication, e.g. of an added benefit, can be derived for the outcome "overall survival", and at most a hint can be derived for each of the other outcomes.

Results

Mortality

Overall survival

There was no statistically significant difference between the treatment arms for the outcome "overall survival". This resulted in no hint of an added benefit of isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone. An added benefit is therefore not proven for this outcome.

Morbidity

Symptoms

The outcomes on symptoms were recorded with the disease-specific instruments European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and EORTC Quality of Life Questionnaire-Multiple Myeloma 20 (QLQ-MY20). The time to first deterioration by ≥ 10 points (scale range from 0 to 100) was considered.

For the outcomes on symptoms, there is either no statistically significant difference to the advantage or disadvantage of isatuximab + pomalidomide + dexamethasone or the effect is no more than marginal.

This resulted in no hint of an added benefit of isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone. An added benefit is therefore not proven for these outcomes.

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

The time to first deterioration by ≥ 15 points (scale range from 0 to 100) was considered for the outcome “health status” (EQ-5D VAS)”.

There was no statistically significant difference between the treatment arms. This resulted in no hint of an added benefit of isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone. An added benefit is therefore not proven for this outcome.

Health-related quality of life

The outcomes on health-related quality of life were recorded with the disease-specific instruments EORTC QLQ-C30 and EORTC QLQ-MY20. The time to first deterioration by ≥ 10 points (scale range from 0 to 100) was considered.

Global health status, physical functioning, role functioning, cognitive functioning, social functioning, body image and future perspective

No statistically significant difference between the treatment arms was shown for the outcomes "global health status", "physical functioning", "role functioning", "cognitive functioning", "social functioning" and "future perspective". This resulted in no hint of an added benefit of isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone. An added benefit is therefore not proven for these outcomes.

Emotional functioning

There was no statistically significant difference between the treatment arms for the outcome "emotional functioning". However, there is an effect modification by the Revised International Staging System (R-ISS stage) (I or II versus III) at study inclusion. There is a hint of lesser benefit for patients with R-ISS stage III at study inclusion; the benefit is not proven for the patients with R-ISS stage I or II.

Side effects

SAEs

There was no statistically significant difference between the treatment arms for the outcome "SAEs". This resulted in no hint of greater harm from isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone; greater or lesser harm is therefore not proven.

Severe AEs (CTCAE grade ≥ 3)

There is a statistically significant difference to the disadvantage of isatuximab + pomalidomide + dexamethasone for the outcome "severe AEs (CTCAE grade ≥ 3)". This resulted in a hint of greater harm from isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone.

Discontinuation due to AEs

For the outcome "discontinuation due to AEs", no analyses are available for the operationalization adequate in the present comparison (discontinuation ≥ 1 drug component). This resulted in no hint of greater or lesser harm from isatuximab + pomalidomide +

dexamethasone in comparison with pomalidomide + dexamethasone; greater or lesser harm is therefore not proven.

Infusion-related reactions

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

Specific AEs

Blood and lymphatic system disorders (System Organ Class [SOC], severe AEs)

A statistically significant difference to the disadvantage of isatuximab + pomalidomide + dexamethasone was shown for the outcome "blood and lymphatic system disorders (SOC, severe AEs)". This resulted in a hint of greater harm from isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone.

Bronchitis (Preferred Term [PT], AEs)

There is a statistically significant difference to the disadvantage of isatuximab + pomalidomide + dexamethasone for the outcome “bronchitis (PT, AEs)”. This resulted in a hint of greater harm from isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + 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 in combination with pomalidomide and dexamethasone in comparison with the ACT is assessed as follows. In the present data situation (barely not statistically significant effect in overall survival, final data cut-off still pending), an added benefit of isatuximab + pomalidomide + dexamethasone over pomalidomide + dexamethasone is not proven for adults with relapsed and refractory multiple myeloma who have received ≥ 2 prior therapies, including lenalidomide and a proteasome inhibitor, and who showed disease progression under the last therapy.

Table 3 shows a summary of probability and extent of the added benefit of isatuximab + pomalidomide + 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 + pomalidomide + dexamethasone – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with relapsed and refractory multiple myeloma who have received ≥ 2 prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression under the last therapy[b]	▪ Bortezomib in combination with dexamethasone, or ▪ lenalidomide in combination with dexamethasone, or ▪ **pomalidomide in combination with dexamethasone**, or ▪ elotuzumab in combination with lenalidomide and dexamethasone, or ▪ elotuzumab in combination with pomalidomide and dexamethasone, or ▪ carfilzomib in combination with lenalidomide and dexamethasone, or ▪ carfilzomib in combination with dexamethasone, or ▪ daratumumab in combination with lenalidomide and dexamethasone, or ▪ daratumumab in combination with bortezomib and dexamethasone	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. It is assumed that high-dose chemotherapy with stem cell transplantation is not an option for the patients at the time point of their current treatment.

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

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

2.2 Research question

The aim of the present report is the assessment of the added benefit of isatuximab in combination with pomalidomide + dexamethasone (isatuximab + pomalidomide + dexamethasone) compared with the ACT in patients with relapsed and refractory multiple myeloma who have received ≥ 2 prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression under the last therapy.

The ACT specified by the G-BA is shown in Table 4.

Table 4: Research question of the benefit assessment of isatuximab + pomalidomide + dexamethasone

Therapeutic indication	**ACT**[a]
Adult patients with relapsed and refractory multiple myeloma who have received ≥ 2 prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression under the last therapy[b]	▪ Bortezomib in combination with dexamethasone, or ▪ lenalidomide in combination with dexamethasone, or ▪ **pomalidomide in combination with dexamethasone**, or ▪ elotuzumab in combination with lenalidomide and dexamethasone, or ▪ elotuzumab in combination with pomalidomide and dexamethasone, or ▪ carfilzomib in combination with lenalidomide and dexamethasone, or ▪ carfilzomib in combination with dexamethasone, or ▪ daratumumab in combination with lenalidomide and dexamethasone, or ▪ daratumumab in combination with bortezomib and dexamethasone
a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b. It is assumed that high-dose chemotherapy with stem cell transplantation is not an option for the patients at the time point of their current treatment. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA's specification of the ACT and did not limit its information retrieval to one of the options listed in Table 4; in Module 4 A, the company provides evidence of the added benefit of pomalidomide in combination with dexamethasone.

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

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on erenumab (status: 1 March 2021)
- bibliographical literature search on isatuximab (last search on 1 March 2021)
- search in trial registries/trial results databases for studies on isatuximab (last search on 1 March 2021)
- search on the G-BA website for isatuximab (last search on 1 March 2021)

to check the completeness of the study pool:

- search in trial registries for studies on isatuximab (last search on 25 May 2021); for search strategies, see Appendix A of the full dossier assessment.

The check did not identify any additional relevant study.

2.3.1 Studies included

The study presented in the following Table 5 was included in the benefit assessment.

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

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
ICARIA-MM; EFC14335 (ICARIA-MM[d])	Yes	Yes	No	Yes [3]	Yes [4,5]	Yes [6-8]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to with this abbreviated form.

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

The study pool concurs with that of the company.

2.3.2 Study characteristics

2.3.2.1 Study and intervention 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 + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ICARIA-MM	RCT, open-label, parallel	Adult patients (≥ 18 years; ECOG PS ≤ 2) with multiple myeloma who have received ≥ 2 prior therapies[b] including ≥ 2 consecutive cycles with lenalidomide and a proteasome inhibitor and who showed disease progression under the last therapy[c]	Isatuximab + pomalidomide + dexamethasone (N = 154) pomalidomide + dexamethasone (N = 153)	Screening: ≤ 28 days treatment: in 28-day cycles until the occurrence of a reason for discontinuation, e.g. disease progression, unacceptable toxicity, death observation[d]: outcome-specific, at most until death, discontinuation of participation in the study or end of study first data cut-off: 11 October 2018/22 November 2018 second data cut-off: 1 October 2020[e]	102 study centres: Australia, Belgium, Canada, Czech Republic, Denmark, France, Germany, Greece, Great Britain, Hungary, Italy, Japan, New Zealand, Norway, Poland, Portugal, Russia, Sweden, Slovakia, South Korea, Spain, Taiwan, Turkey, USA Period: 01/2017–ongoing[f]	Primary: PFS secondary: overall survival, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: isatuximab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Induction therapy followed by stem cell transplantation and consolidation/maintenance therapy is considered as one line of treatment.
c. The progression had to have occurred during the last therapy or within 60 days of the end of the last therapy before study entry, i.e. refractory to the last line of treatment. The patient population comprises the following 2 categories: 1: Refractory disease: patients who have not responded to any prior line of treatment, but achieved at least one MR in the prior line (i.e. a primarily refractory disease was not included). 2: Relapsed and refractory disease: patients who had relapsed from ≥ 1 prior line of treatment and were refractory until the last line of treatment. Patients could have been refractory to other previous lines of treatment.
d. Outcome-specific information is provided in Table 8.
e. Planned subsequently (amendment 6 of 21 April 2021), only overall survival and AEs.
f. Recruitment completed.

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

Table 7: Characteristics of the intervention – RCT, direct comparison: isatuximab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone (multipage table)

Study	Intervention	Comparison
ICARIA-MM	Isatuximab: 10 mg/kg body weight IV cycle 1: day 1, 8, 15 and 22 from cycle 2 onwards: day 1 and 15 premedication before infusion: dexamethasone (see below), paracetamol and diphenhydramine according to SPC of isatuximab as well as ranitidine 50 mg, IV	–
	Pomalidomide: 4 mg orally once daily, on days 1–21	Pomalidomide: 4 mg orally once daily, on days 1–21
	Dexamethasone: patients < 75 years 40 mg orally[a] once daily, on day 1, 8, 15 and 22 patients ≥ 75 years 20 mg orally[a] once daily, on day 1, 8, 15 and 22 length of cycle: 28 days	Dexamethasone: patients < 75 years 40 mg orally[a] once daily, on day 1, 8, 15 and 22 patients ≥ 75 years 20 mg orally[a] once daily, on day 1, 8, 15 and 22 length of cycle: 28 days
	Dose adjustment in case of toxicity, e.g. Neutropenia or thrombocytopenia ▪ isatuximab: no dose adjustment, postponement of next cycle until improvement; discontinuation if no improvement occurs by day 14 of the next cycle ▪ pomalidomide: dose reduction in 1-mg steps; discontinuation in case of persisting toxicity or certain events (e.g. deep vein thrombosis CTCAE grade ≥ 4) ▪ dexamethasone (< 75 years): stepwise dose reduction to 20 mg, 12 mg, 8 mg or 4 mg; discontinuation in case of persistent toxicity or certain events (e.g. change of mood CTCAE grade ≥ 2) ▪ dexamethasone (≥ 75 years): stepwise dose reduction to 12 mg, 8 mg or 4 mg; discontinuation in case of persistent toxicity or certain events (e.g. change of mood CTCAE grade ≥ 2) treatment with the remaining drug components could be continued after discontinuation of a drug component.	

Table 7: Characteristics of the intervention – RCT, direct comparison: isatuximab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone (multipage table)

Study	Intervention	Comparison
	Pretreatment ▪ pretreatment with 2 ≥ prior therapies including ≥ 2 consecutive cycles with lenalidomide and a proteasome inhibitor (alone or in combination)[b] **non-permitted pretreatment** ▪ treatment with pomalidomide ▪ treatment (including dexamethasone) of the multiple myeloma with 14 days before randomization ▪ treatment with monoclonal anti-CD38 antibodies with progression at the end of treatment or within 60 days after end of treatment or failure to achieve at least 1 MR under the treatment **permitted concomitant treatment** ▪ antithrombotic prophylaxis ▪ prophylactic treatment with granulocyte colony-stimulating factors **non-permitted concomitant treatment** ▪ systemic corticosteroids of the study medication except dexamethasone ▪ strong CYP1A2 inhibitors (e.g. cinofloxacin)	

a. IV, if oral intake was not possible.
b. Treatment with lenalimode and a proteasome inhibitor (bortezomib, carfilzomib or ixazomib) had to have failed according to one of the following 3 criteria: 1) progression during treatment or within 60 days after end of treatment; 2) progression within 6 months after treatment discontinuation in case of at least partial response; 3) intolerable toxicity after at least 2 consecutive cycles of a therapy.

CD38: cluster of differentiation 38; CTCAE: Common Terminology Criteria for Adverse Events; CYP1A2: cytochrome P450 1A2; IV: intravenous; RCT: randomized controlled trial

ICARIA-MM is an ongoing RCT that compares isatuximab + pomalidomide + dexamethasone with pomalidomide + dexamethasone. The study investigates adults with refractory or relapsed and refractory multiple myeloma who have received at least 2 prior therapies including lenalidomide and a proteasome inhibitor. They had to have relapsed after treatment with lenalidomide or a proteasome inhibitor or had to be refractory to the treatment or had to have developed intolerable toxicity. Moreover, patients had to show progression of the disease under the last therapy. This progression had to have occurred during the last therapy or within 60 days of the end of the last therapy before study entry, i.e. patients were refractory to the last line of treatment.

The population of the ICARIA-MM study thus comprises the following 2 categories of the disease:

- Refractory disease: patients who have not responded to any prior line of treatment, but achieved at least one MR according to [9] in at least one prior line (i.e. a primarily refractory disease was not included). According to international consensus (see Appendix

F in the study protocol on [3]), this group is also referred to as „relapsed and refractory myeloma“

- Relapsed and refractory disease: patients who had relapsed from at least one prior line of treatment and were refractory to the last line of treatment. Patients could have been refractory to other previous lines of treatment. According to international consensus (see Appendix F in the study protocol on [3]), this group is also referred to as „relapsed myeloma“

The therapeutic indication specified in the approval, i.e. relapsed and refractory multiple myeloma, is thus represented in the ICARIA-MM study.

According to the inclusion criteria, patients with or without prior stem cell transplantation could be included. According to the therapeutic algorithm, it is assumed that, in the present therapeutic indication, high-dose chemotherapy with subsequent stem cell transplantation was not indicated for patients without previous stem cell transplantation at study inclusion (see e.g. [10,11]).

307 patients were randomly assigned either to treatment with isatuximab + pomalidomide + dexamethasone (154 patients) or to treatment with pomalidomide + dexamethasone (153 patients). Stratification factors were age (< 75 years vs. ≥ 75 years) and number of prior therapies (2 or 3 vs. ≥ 4 lines of treatment). Neither patients nor study staff are blinded to the treatment.

In both study arms, treatment took place in 28-day cycles until the occurrence of a reason for discontinuation (e.g. disease progression, unacceptable toxicity or withdrawal of consent). Treatment with the remaining drug components could be continued after discontinuation of a drug component. The study protocol did not intend a switch from treatment of the control arm to treatment of the intervention arm (treatment switching). There were no restrictions regarding subsequent therapies after the end of the study medication (an overview of the subsequent antimyeloma therapies can be found in Table 11).

The application of isatuximab, pomalidomide and dexamethasone in both study arms largely corresponded to the recommendations of the SPC for isatuximab and pomalidomide [12,13]. Based on the information in the European Public Assessment Report (EPAR) [7], the fact that isatuximab was administered in a variable dilution volume in the ICARIA-MM study and not in a fixed dilution volume as stated in the SPC [13], is not considered relevant. The SPC for isatuximab does not mention the H2 antagonist ranitidine as premedication. This is presumably associated with the suspension of the approval of ranitidine due to contamination ([14]). However, it is assumed that the study results are usable for the benefit assessment despite the administration of ranitidine in the ICARIA-MM study.

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

2.3.2.2 Data cut-offs

ICARIA-MM is an ongoing study whose recruitment has been completed.

Results on 2 data cut-offs are available for the ICARIA-MM study:

- First data cut-off: 11 October 2018/22 November 2018 – planned data cut-off for PFS to obtain the approval with analyses on all outcomes (11 October 2018: "overall survival", "PFS", "symptoms" and "health-related quality of life", 22 November 2018: outcomes on side effects)
- Second data cut-off: 1 October 2020 – with protocol amendment 6, of 21 April 2020, inserted data cut-off for "overall survival" (90% of the 220 deaths required for the final analysis) with analyses on "overall survival" and the outcomes on side effects.

The final analysis for overall survival is planned when 220 deaths will have occurred.

In the present benefit assessment, the results of the first data cut-off were used for the outcomes on morbidity, symptoms and health-related quality of life; the results of the second data cut-off were used for overall survival and the outcomes on side effects, as these cover the individual longest available observation periods. This deviates from the company's approach, which based its assessment on the first data cut-off and presented the results of the second data cut-off as supplementary information. It justified its approach by claiming that the second data cut-off only reports results of the outcome "overall survival" and the outcomes on safety and tolerability, and was not requested by the regulatory authority in the context of the approval. The approach of the company was not appropriate. According to the statistical analysis plan, the final analysis should only comprise overall survival and the outcomes on side effects. However, the study documents provide no information as to whether the recording of this outcome was terminated after the first data cut-off. For the second data cut-off, analyses should thus have been conducted and submitted for all outcomes in accordance with the dossier template. The analyses on the first data cut-off were nevertheless considered usable for the following reasons: At the time of the first data cut-off, the majority of patients were no longer receiving treatment (87 [56%] vs. 114 [75%] patients). Moreover, the time between the end of recruitment and the data cut-off was approx. 8 months. Events additionally occurring between the first and the second data cut-off would therefore only occur after this period. However, it can be seen from the Kaplan-Meier curves that the majority of the events occurred before the time point "8 months" in each case (see Appendix D). Overall, it is therefore not assumed that the effects in the outcomes "morbidity", "symptoms" and "health-related quality of life" would change relevantly between the first and the second data cut-off.

2.3.2.3 Planned treatment duration and follow-up observation

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

Table 8: Planned duration of follow-up – RCT, direct comparison: isatuximab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone

Study **outcome category** **outcome**	**Planned follow-up observation**
ICARIA-MM	
Mortality	
Overall survival	Until withdrawal of consent, lost to follow-up, death, or end of study
Morbidity	
Symptoms (EORTC QLQ-C30, EORTC QLQ-MY20), health status (EQ-5D VAS)	Up to a maximum of 60 ± 5 days after the last administration of the study medication
Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-MY20)	Up to a maximum of 60 days after the last administration of the study medication
Side effects	
All outcomes in the category of side effects	Up to a maximum of 30 days after the last administration of the study medication[a]
a. AEs and SAEs considered to be caused by the study medication were observed until withdrawal of consent, lost to follow-up, death or end of study. However, the analysis considered in the present benefit assessment is based on AEs which occurred between the start and 30 days after the last dose of study treatment (treatment-emergent AEs).	
AE: adverse event; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-MY20: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Multiple Myeloma Module 20; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale	

The observation periods for the outcomes “morbidity”, “health-related quality of life” and “side effects” were systematically shortened because they were only recorded for the time period of treatment with the study medication (plus a maximum of 30 days or 60 days). To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to record these outcomes over the total period of time, as was the case for survival.

2.3.2.4 Characteristics of the study population

Table 9 shows the characteristics of the patients in the study included.

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

Study characteristic category	Isatuximab + pomalidomide + dexamethasone N[a] = 154	Pomalidomide + dexamethasone N[a] = 153
ICARIA-MM		
Age [years], mean (SD)	67 (9)	65 (10)
Sex [F/M], %	42/58	54/46
Family origin, n (%)		
Caucasian	118 (77)	126 (82)
Black/African American	1 (1)	3 (2)
Asian	21 (14)	15 (10)
Hawaiian or other Asian-Pacific origin	2 (1)	1 (1)
Not reported/unknown	12 (8)	8 (5)
ECOG PS on study entry, n (%)		
0	55 (36)	69 (45)
1	83 (54)	68 (44)
2	16 (10)	16 (10)
Disease stage on study entry (R-ISS), n (%)		
I	39 (25)	31 (20)
II	99 (64)	98 (64)
III	16 (10)	24 (16)
Time since first diagnosis of the multiple myeloma [years], median [min; max]	4.5 [0.6; 18.4]	4.1 [0.5; 20.5]
Cytogenetic risk group, n (%)		
High risk[b]	24 (16)	36 (24)
Standard risk	103 (67)	78 (51)
Unknown/data not available	27 (18)	39 (25)
Type of myeloma at diagnosis, n (%)		
IgG	102 (66)	100 (65)
IgA	34 (22)	41 (27)
IgM	2 (1)	0 (0)
IgD	0 (0)	0 (0)
IgE	0 (0)	0 (0)
Only kappa light chains	8 (5)	7 (5)
Only lambda light chains	7 (5)	4 (3)
Unknown/not detected	1 (1)	1 (1)

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

Study characteristic category	Isatuximab + pomalidomide + dexamethasone N[a] = 154	Pomalidomide + dexamethasone N[a] = 153
Prior lines of treatment, n (%)		
2 or 3	102 (66)	101 (66)
> 3	52 (34)	52 (34)
Number and type of pretreatments, n (%)		
Antineoplastic and immunomodulatory pretreatment	11 (7)	4 (3)
Alkylating agents	139 (90)	148 (97)
Proteasome inhibitors	154 (100)	153 (100)
Immunomodulators	154 (100)	153 (100)
Histone deacetylase inhibitors	4 (3)	7 (5)
Monoclonal antibodies	2 (1)	2 (1)
Relapsed and refractory myeloma	154 (100)	153 (100)
Refractory to last treatment regimen, n (%)	150 (97)	151 (99)
Refractory to proteasome inhibitors, n (%)		
Yes	118 (77)	115 (75)
No	36 (23)	38 (25)
Refractory to immunomodulatory drugs, n (%)		
Yes	147 (95)	144 (94)
No	7 (5)	7 (5)
Refractory to lenalidomide in the last treatment regimen, n (%)		
Yes	142 (92)	138 (90)
No	12 (8)	15 (10)
Prior transplantation, n (%)		
≥ 1 transplantations	83 (54)	90 (59)
≥ 2 transplantations	27 (18)	22 (14)
Treatment discontinuation[c] at first data cut-off, n (%)	87 (56[d])[e]	114 (75[d])[f]
Treatment discontinuation[c] at second data cut-off, n (%)	125 (81)[g]	137 (90)[h]
Study discontinuation, n (%)	ND	ND

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Either deletion (del) (17p), t (4;14) or t (14;16) available.
c. All drug components.
d. Institute's calculation.
e. 66 discontinuations due to progression of the disease, 11 discontinuations due to AEs.
f. 88 discontinuations due to progression of the disease, 19 discontinuations due to AEs.
g. 94 discontinuations due to progression of the disease, 18 discontinuations due to AEs.
h. 109 discontinuations due to progression of the disease, 21 discontinuations due to AEs.

AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; Ig: immunoglobulin; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; R-ISS: Revised International Staging System; SD: standard deviation

The patient characteristics are largely comparable between the study arms. The mean age of the patients was 66 years. 64% of the patients had R-ISS stage II, and slightly more than 10% had R-ISS stage III. At baseline, a median of 4 years had passed since the initial diagnosis of the multiple myeloma. All patients were pre-treated with the immunomodulator lenalidomide and a proteasome inhibitor and almost all were refractory to the last line of therapy. There were slight differences between the treatment arms for sex (42% vs. 54% female), Eastern Cooperative Oncology Group Performance Status (ECOG PS) (36% vs. 45% in stage 0 and 54% vs. 44% in stage 1) and the cytogenetic risk (16% vs. 24% with high risk and 67% vs. 51% with standard risk).

2.3.2.5 Treatment duration and observation period as well as subsequent therapies

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

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

Study **duration of the study phase** **outcome category**	**Isatuximab + pomalidomide + dexamethasone** **N = 154**	**Pomalidomide + dexamethasone** **N = 153**
ICARIA-MM		
Treatment duration [months] first data cut-off[a]		
Total, median [Q1; Q3]	9.4 [4.4; 12.0]	5.5 [2.5; 11.0]
Isatuximab, median [min; max]	9.4 [0.2; 17.2]	–
Pomalidomide, median [min; max]	9.2 [0.2; 17.2]	5.5 [0.2; 17.0]
Dexamethasone, median [min; max]	9.4 [0.2; 17.7]	5.5 [0.2; 17.0]
Observation period [months] first data cut-off		
Overall survival		
Median [Q1; Q3]	12 [ND]	12 [ND]
Symptoms and morbidity	ND	ND
Health-related quality of life	ND	ND
Side effects	ND	ND
Treatment duration [months] second data cut-off[a]		
Total, median [min; max]	11.0 [0.2; 39.6]	5.5 [0.2; 38.9]
Isatuximab, median [min; max]	10.8 [0.2; 39.6]	–
Pomalidomide, median [min; max]	9.4 [0.2; 39.3]	5.5 [0.2; 38.9]
Dexamethasone, median [min; max]	10.6 [0.2; 39.6]	5.5 [0.2; 37.0]
Observation period [months] second data cut-off		
Overall survival		
Median [Q1; Q3]	35 [ND][b]	
Symptoms and morbidity	No results presented	
Health-related quality of life	No results presented	
Side effects	ND[c]	ND[c]

a. Data refer to the safety population (152 vs. 149 patients).
b. No data per treatment arm.
The analysis for the outcomes on side effects is based on AEs which occurred between the start and 30 days after the last dose of study treatment (treatment-emergent AEs). Based on these data, an observation period of 12.0 months vs. 6.4 months was estimated.

AE: adverse event; max.: maximum; min: minimum; N: number of randomized patients; ND: no data; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation

The treatment duration is not the same for the individual components of the study medication, as they could be discontinued independently of one another. The differences in treatment duration of the individual drugs are small, however. It is therefore possible to conduct a meaningful comparison of the median treatment duration between the study arms. Median

treatment duration was longer in the isatuximab + pomalidomide + dexamethasone arm than in the pomalidomide + dexamethasone arm (first data cut-off: 9.4 months versus 5.5 months; second data cut-off: 11.0 months versus 5.5 months).

There was no information on the observation period for overall survival. At the first data cut-off, this median observation period was 12 months in both arms. At the second data cut-off, the common median observation period was 35 months for both arms; data per treatment arm are not available.

Module 4 A provides no information on the observation period for "symptoms", "health-related quality of life" and the outcomes on side effects. Since the collection of these outcomes was terminated 30 days or 60 days after the end of study medication, a similar difference in the observation duration between the treatment arms as for the treatment duration can be assumed.

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

Table 11: Information on the subsequent antimyeloma therapies – RCT, direct comparison: isatuximab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone; second data cut-off (1 October 2020)

Study drug class	**Patients with subsequent therapy n (%)**	
	isatuximab + pomalidomide + dexamethasone N = 154	**pomalidomide + dexamethasone N = 153**
ICARIA-MM		
Total	92 (59.7)	110 (71.9)
Alkylating drugs	64 (69.6)	52 (47.3)
Anthracyclines and related substances	7 (7.6)	10 (9.1)
Histone deacetylase inhibitors	4 (4.3)	4 (3.6)
Immunomodulators	31 (33.7)	34 (30.9)
Corticosteroids	82 (89.1)	85 (77.3)
Monoclonal antibodies	26 (28.3)	68 (61.8)
Proteasome inhibitors	61 (66.3)	60 (54.5)
Vinca alkaloids and analogues	2 (2.2)	3 (2.7)
Other	34 (37.0)	21 (19.1)

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

After discontinuation of the study treatment, subsequent anti-myeloma therapies could be administered without restriction. In the isatuximab + pomalidomide + dexamethasone arm, the proportion of patients with ≥ 1 subsequent anti-myeloma therapies was smaller than in the pomalidomide + dexamethasone arm (60% vs. 72%). The largest differences between the treatment arms were shown for alkylating agents (70% vs. 47% of patients with ≥ 1 subsequent

anti-myeloma therapies) and monoclonal antibodies (28% vs. 62% of patients with ≥ 1 subsequent anti-myeloma therapies). In most cases, these monoclonal antibodies were daratumumab (like isatuximab, an antibody against cluster of differentiation 38 [CD38]).

2.3.2.6 Risk of bias across outcomes (study level)

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

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

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
ICARIA-MM	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

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

Limitations resulting from the open-label study design are described in Section 2.4 with the outcome-specific risk of bias.

2.3.2.7 Transferability of the study results to the German health care context

The company stated that the ICARIA-MM study was predominantly conducted in countries that belong to the Western world in terms of their social systems, culture and origin. Moreover, the company pointed out that one centre was in Germany and that the slightly higher proportion of male patients reflected the slightly higher disease rate compared to women. It can therefore be assumed that the study population reflects 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.

2.4 Results on added benefit

2.4.1 Outcomes included

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

- Mortality
  - overall survival

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

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

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

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

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

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. The following events (MedDRA coding) are considered: "blood and lymphatic system disorders (SOC, severe AEs)", "bronchitis (PT, AEs)".
c. No usable results available; data are only available for the discontinuation of all drug components.
d. No usable results, see justification in the text.

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

Notes on the included outcomes and analyses

Symptoms and health-related quality of life

- In its dossier, the company presented responder analyses for the proportion of patients with a change by ≥ 10 points and by ≥ 15% of the scale range (respective scale range 0 to -100) for the EORTC QLQ-C30 and the EORTC QLQ-MY20. As explained in the *General Methods* of the Institute ([1,15]), for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to a predefined value of at least 15% of the scale range of an instrument (in post-hoc analyses exactly 15% of the scale range). For the EORTC QLQ-C30 and its additional modules, the analysis with a previously accepted response threshold of 10 points is considered a sufficient approximation to an analysis with a 15% threshold (15 points) in certain constellations and is used for the benefit assessment (for explanation see [16]). Regardless of this, analyses with the previously accepted response threshold of 10 points for the EORTC QLQ-C30 as well as all additional modules of the EORTC will primarily be used for a

transitional period until the adjusted module templates for the dossier come into force (see FAQs of the G-BA [17]).

- In its dossier, the company presented responder analyses for the time to deterioration by ≥ 7 or ≥ 10 points (scale range 0-100) for the outcome "health status" (EQ-5D VAS). These were not used for the present benefit assessment, but are presented as supplementary information in Appendix A. Moreover, the company submitted responder analyses with the response criterion of 15% of the scale range in Appendix 4 G of the dossier. These are used for the derivation of the added benefit; however, the company presented no subgroup analyses for this purpose in Module 4 A.
- The company presented the following operationalizations for the outcomes of the EORTC QLQ-C30, the EORTC QLQ-MY20 and the EQ-5D VAS:
  - Time to first deterioration
  - Time to permanent deterioration
  - Time to first improvement
  - Time to permanent improvement

  Of these operationalizations, the time to first deterioration was used.

  Due to the progressive course of the disease expected in the present therapeutic indication, an analysis of the deterioration of the health status is primarily relevant for the present benefit assessment.

  The analyses on the time to first deterioration were preferred to the analyses on the time to permanent deterioration, as no information was available on the operationalization of the time to permanent deterioration and the description of the analyses. Thus, for instance, it remains unclear whether a deterioration is considered permanent if the response criterion is also fulfilled in all subsequent observations, and how patients who had a (then one-time) deterioration at the last time point of documentation time were dealt with.

Outcomes on side effects

- For the outcomes on side effects, the company provided supplementary analyses in Module 4 A, Appendix G, which exclude events that are assigned to the SOC "benign, malignant and unspecified neoplasms (incl. cysts and polyps)" according to the Medical Dictionary for Regulatory Activities (MedDRA). These analyses are not used because the events in this SOC do not represent a progression of the underlying disease, but mostly secondary primary tumours (e.g. skin cancer); an exclusion of these events is thus not adequate. Moreover, it is not adequate that the company did not exclude the PT "disease progression" (SOC "general disorders and administration site conditions"; all events are deaths) from the calculation of the overall rates of the superordinate outcomes on side effects. However, it is assumed that this procedure has no impact relevant for the conclusion (as their proportion is small in relation to the overall rate).

- According to the study protocol, laboratory values for side effect outcomes were only reported as AEs if they resulted in treatment discontinuation or dose modification or were an SAE or Adverse Event of Special Interest (AESI). This potentially led to incomplete recording, especially of the severe AEs. For instance, the proportion of patients with neutropenia from the results on laboratory values is significantly higher than from the AE recording (for the first data cut-off, neutropenia with CTCAE grade 3 or 4 was reported in 85% vs. 70% of patients as a laboratory value [6] and in 45% vs. 32% of patients as AE). This "underreporting" is also addressed by the Food and Drug Administration (FDA) ([18]), but they accept this approach with reference to the fact that laboratory values are generally not fully reported in AE analyses. Among other things, the European Medicines Agency (EMA) addressed the company's approach by reporting both the results from the AE recording and the laboratory values in the SPC. Overall, the analyses on side effects are assessed as usable in the present assessment, but the informative value of the results on severe side effects is limited; this is taken into account in the assessment of the certainty of conclusions (see Section 2.4.2).
- For the outcome "discontinuation due to AEs", the company only presented analyses of the time to discontinuation of all drug components in Module 4 A. Analyses for discontinuation of at least 1 drug component are missing. According to the study protocol, patients could continue treatment with the remaining drugs after discontinuation of individual drugs. An analysis on the discontinuation of all drug components alone cannot be meaningfully interpreted in the present data situation (3 drug components in the intervention arm and 2 drug components in the control arm). Regardless of this, analyses on the discontinuation of at least 1 drug component are to be preferred, 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 are required for the benefit assessment.
- The dossier contained no usable data for the outcome "infusion-related reactions".

  In Module 4 A, the company presented several operationalizations for the specific AE "infusion-related reactions", which address this AE:

  - Reactions associated with an infusion (PT, AEs, version 21.0) – referred to by the company as "infusion reaction" (in the study report: PT "infusion related reaction") in Module 4.
  - Infusion reactions with CTCAE grade ≥ 3 as a subset of the AESI defined a priori, where infusion reactions included various PTs ("cytokine release syndrome, infusion-related reaction, anaphylactic reaction, hypersensitivity")

  The study protocol describes that infusion reactions were defined as AEs that typically occurred within 24 hours after the infusion and which, according to the investigators' assessment, were associated with isatuximab (a predefined compilation of PTs could be found in the study protocol). It is unclear whether these criteria also applied to the PT

"infusion related reaction". However, it is assumed that these criteria at least had a significant influence on the recording of the PT. The operationalizations presented by the company were not suitable for the following reasons:

- Due to the open study design (without placebo infusion) and a regular IV administration only in the intervention arm, events in the PT "infusion related reaction under the study medication" could basically only be recorded in the intervention arm (IV administration in the control arm was only possible in exceptional cases, unclear whether it took place); the 2 events in the control arm were infusion reactions under the subsequent therapy daratumumab.
- The study protocol states that whenever it was possible to make a clinical diagnosis of an infusion reaction (i.e. to select the PT "cytokine release syndrome", "infusion-related reaction", "anaphylactic reaction", "hypersensitivity"), this diagnosis was to be reported as an AE (e.g. PT "infusion-related reactions") rather than the underlying individual symptoms, which were recorded in a separate documentation form (Case Report Form [CRF]). Individual symptoms were not included in the general AE analysis of Treatment-Emergent Adverse Events (TEAE) (but are reported separately in the study report and only for the intervention arm, see Table 28 of the full dossier assessment). The events under the affected symptoms (e.g. the PT "dyspnoea" and the PT "cough") were therefore not fully recorded in the analyses on PT/SOC submitted by the company in Module 4 A; this is taken into account in the assessment of the certainty of conclusions of the specific AEs (see Section 2.4.2).
- Moreover, the classification into severity grades for the PT was not based on the specific CTCAE criteria for the individual symptoms, but on the (non-specific) CTCAE criteria for the PT "infusion-related reaction". The study report shows that the use of the symptom-specific criteria results in 8 patients with an event instead of 4 patients with an event of CTCAE grade ≥ 3; the number of patients with an event in the superordinate AE outcome "severe AEs" is thus potentially underestimated in the isatuximab arm.

In summary, no usable data are available for the AE "infusion-related reactions" due to the reasons mentioned above. In order to obtain the comparative data required for the benefit assessment, it is necessary to consider all symptomatic AEs (e.g. "chills", "dyspnoea", "cough", "nausea", regardless of whether they are infusion-related or not) within the framework of the TEAE analysis. For this purpose, the respective symptoms had to be included in the TEAEs via the corresponding PT (e.g. "dyspnoea"). Overall, a standardization of the recording of (potential) infusion-related reactions in clinical trials seems necessary to enable comparisons across different clinical trials.

In addition to the lack of usable data for the AE "infusion-related reactions", the way the EORTC records data is not suitable to reflect the impact of these side effects of isatuximab on symptoms (such as "dyspnoea") and the quality of life. The questionnaires (EORTC QLQ-C30, EORTC QLQ-MY20 and EQ 5D VAS) were completed at the start

of each 28-day cycle (day 1) prior to the administration of the medication, each of them recording the symptoms/quality of life in the last week. Since the isatuximab infusions from cycle 2 onwards were administered on days 1 and 15 (and not daily from day 1 to day 22 like the other [oral] doses in the intervention and control arms), the infusion-related reactions therefore did not fall within the time period queried by the questionnaire.

2.4.2 Risk of bias

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

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

Study		Outcomes											
	Study level	Overall survival	Symptoms (EORTC QLQ-C30)	Symptoms (EORTC QLQ-MY20)	EQ-5D VAS	Health-related quality of life (EORTC QLQ-C30)	Health-related quality of life (EORTC QLQ-MY20)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Infusion-related reactions	Specific AEs[a], [b]
ICARIA-MM	N	N	H[c, d, e, f]	H[c, d, e, f]	H[c, d, e, f]	H[c, d, e, f]	H[c, d, e, f]	H[e, g]	H[e, g]	_[h]	_[i]	H[c, e, g]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. The following events (MedDRA coding) are considered: “blood and lymphatic system disorders (SOC, severe AEs)", “bronchitis (PT, AEs)".
c. Lack of blinding (patient) in subjective recording of outcomes. In case of the specific AEs, this applies to the non-severe/non-serious AEs.
d. Clearly decreasing response to questionnaires in the course of the study, which cannot be explained by death alone.
e. Large difference in median treatment duration (and consequently in observation duration) between the intervention arm (9.4 months for EORTC QLQ and EQ 5D VAS, 11.0 months for outcomes on AEs) and the control arm (5.5 months for EORTC QLQ and EQ 5D VAS as well as for outcomes on AEs).
f. Differing data on the analysed population: according to Module 4 A, the analysis was to be based on the ITT population, but according to the SAP, it was to include patients from the safety population who had at least one measurement each at baseline and thereafter.
g. Incomplete observations for potentially informative reasons.
c. No usable results available; data are only available for the discontinuation of all drug components, see Section 2.4.1.
b. No usable data available, see Section 2.4.1.

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

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

For the results of the outcomes of symptoms, health status and health-related quality of life, the risk of bias is rated as high, among other things due to the open-label study design and the different median observation durations (Table 14). This classification also concurs with the assessment of the company.

For the side effect outcomes, the risk of bias of the results is rated as high due to different median observation durations and incomplete observations for potentially informative reasons. For the specific non-severe/non-serious AEs, the lack of blinding additionally contributes to the high risk of bias (Table 14). This classification deviates from the assessment of the company, which postulated a low risk of bias for the results of the severe AEs and the SAEs. For the results of the specific non-severe/non-serious AEs, the assessment is in line with that of the company, whereby the company assessed the risk of bias for the overall rate of AEs and, among other things, cited the lack of blinding as a reason for a risk of bias.

The certainty of conclusions for side effects is limited due to additional aspects (see Section 2.4.1 “Handling of laboratory values for the severe AEs and documentation of events in connection with infusion-related reactions”), but this has no consequences for the present assessment, as there is already a reduced certainty of conclusions for the outcomes concerned due to the high risk of bias and the analyses are usable for the benefit assessment despite their deficiencies.

2.4.3 Results

Table 15 summarizes the results on the comparison of isatuximab + pomalidomide + dexamethasone compared with pomalidomide + dexamethasone in patients with relapsed and refractory multiple myeloma who have received ≥ 2 prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression under the last therapy. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company’s dossier.

Common AEs, common severe AEs (CTCAE grade ≥ 3) and common SAEs are presented in Appendix C of the full dossier assessment. Kaplan-Meier curves on the event time analyses and a forest plot on subgroup analyses can be found in Appendix D; Kaplan-Meier curves for the outcomes on side effects are missing for the second data cut-off considered in the present benefit assessment.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: isatuximab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone (multipage table)

Study outcome category outcome	Isatuximab + pomalidomide + dexamethasone		Pomalidomide + dexamethasone		Isatuximab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI][a]; p-value[b]
ICARIA-MM					
Mortality (second data cut-off: 1 October 2020)					
Overall survival	154	24.6 [20.3; 31.3] 93 (60.4)	153	17.7 [14.4; 26.2] 105 (68.6)	0.76 [0.57; 1.01]; 0.056
Morbidity (first data cut-off: 11 October 2018)					
Symptoms (EORTC QLQ-C30) - time to first deterioration by ≥ 10 points[c]					
Fatigue	154	2.3 [1.9; 3.6] 114 (74.0)	153	2.8 [2.0; 3.8] 104 (68.0)	1.00 [0.76; 1.31]; 0.990
Nausea and vomiting	154	NA [10.7; NC] 60 (39.0)	153	NA [11.3; NC] 57 (37.3)	0.97 [0.67; 1.39]; 0.851
Pain	154	5.6 [3.2; 7.7] 93 (60.4)	153	6.1 [3.8; 9.8] 80 (52.3)	1.09 [0.81; 1.47]; 0.579
Dyspnoea	154	4.8 [2.9; 12.5] 86 (55.8)	153	6.6 [3.8; NC] 75 (49.0)	1.10 [0.81; 1.51]; 0.541
Insomnia	154	6.6 [4.7; 9.5] 87 (56.5)	153	9.7 [4.7; NC] 69 (45.1)	1.26 [0.92; 1.72]; 0.158
Appetite loss	154	5.8 [4.7; 8.4] 88 (57.1)	153	10.7 [6.5; NC] 68 (44.4)	1.32 [0.96; 1.82]; 0.085
Constipation	154	8.1 [5.0; NC] 76 (49.4)	153	4.3 [2.9; 7.9] 85 (55.6)	0.72 [0.53; 0.99]; 0.041
Diarrhoea	154	13.0 [7.0; NC] 69 (44.8)	153	NA [NC; NC] 46 (30.1)	1.51 [1.04; 2.20]; 0.030
Symptoms (EORTC QLQ-MY20) - time to first deterioration by ≥ 10 points[c]					
Disease-related symptoms	154	7.9 [5.6; NC] 79 (51.3)	153	NA [8.4; NC] 60 (39.2)	1.28 [0.91; 1.79]; 0.153
Side effects	154	6.9 [4.2; 9.5] 83 (53.9)	153	7.6 [5.6; NC] 70 (45.8)	1.20 [0.87; 1.65]; 0.261
Health status (EQ-5D VAS) – time to first deterioration by ≥ 15 points[d]					
EQ-5D VAS	154	10.5 [7.0; 15.5] 74 (48.1)	153	15.1 [11.1; NC] 59 (38.6)	1.18 [0.84; 1.67]; 0.337

Table 15: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: isatuximab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone (multipage table)

Study outcome category outcome	Isatuximab + pomalidomide + dexamethasone		Pomalidomide + dexamethasone		Isatuximab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI][a]; p-value[b]
Health-related quality of life (first data cut-off; 11 October 2018)					
Health-related quality of life (EORTC QLQ-C30) - time to first deterioration by ≥ 10 points[d]					
Global health status	154	4.4 [3.0; 7.3] 93 (60.4)	153	3.5 [2.5; 6.1] 87 (56.9)	0.93 [0.69; 1.25]; 0.624
Physical functioning	154	5.6 [3.9; 8.6] 91 (59.1)	153	5.2 [4.1; 7.9] 82 (53.6)	0.94 [< 0.69; 1.27], 0.658
Role functioning	154	4.4 [2.9; 7.0] 94 (61.0)	153	3.8 [2.8; 4.8] 96 (62.7)	0.84 [0.63; 1.13]; 0.253
Emotional functioning	154	7.1 [4.7; NC] 80 (51.9)	153	9.5 [5.6; NC] 69 (45.1)	1.12 [0.81; 1.55]; 0.479
Cognitive functioning	154	5.7 [3.8; 9.7] 86 (55.8)	153	6.1 [3.8; 10.6] 80 (52.3)	1.00 [0.74; 1.36]; 0.999
Social functioning	154	2.9 [2.0; 4.8] 103 (66.9)	153	4.7 [2.9; 9.3] 87 (56.9)	1.22 [0.91; 1.63]; 0.174
Health-related quality of life (EORTC QLQ-MY20) - time to first deterioration by ≥ 10 points[d]					
Body image	154	12.1 [8.3; NC] 67 (43.5)	153	13.9 [7.5; NC] 60 (39.2)	1.14 [0.80; 1.62]; 0.457
Future perspective	154	5.5 [2.8; 13.6] 84 (54.5)	153	6.6 [3.0; 10.2] 80 (52.3)	1.01 [0.74; 1.37]; 0.960
Side effects (second data cut-off: 1 October 2020)					
AEs (supplementary information)	152	0.2 [0.2; 0.2] 151 (99.3)	149	0.3 [0.3; 0.5] 146 (98.0)	–
SAEs	152	6.0 [2.8; 9.8] 111 (73.0)	149	6.6 [3.8; 14.9] 90 (60.4)	1.27 (0.96; 1.68), 0.097
Severe AEs[e]	152	0.9 [0.8; 1.1] 138 (90.8)	149	1.6 [1.0; 2.8] 112 (75.2)	1.50 [1.17; 1.94]; 0.002
Discontinuation due to AEs	152	ND[f]	149	ND[f]	
Infusion-related reactions	No usable data available[g]				

Table 15: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: isatuximab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone (multipage table)

Study outcome category outcome	Isatuximab + pomalidomide + dexamethasone		Pomalidomide + dexamethasone		Isatuximab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI][a]; p-value[b]
Blood and lymphatic system disorders (SOC, severe AEs[h])	152	0.7 [0.6; 0.8][i] 94 (61.8)	149	1.0 [0.8; 1.9][i] 63 (42.3)	1.68 [1.22; 2.31]; 0.001
Bronchitis (PT, AEs)	152	12.5 [4.5; NC][i] 41 (27.0)	149	NA [27.2; NC][i] 17 (11.4)	2.43 [1.38; 4.28]; 0.002

a. Cox proportional hazards model stratified by age (< 75 years vs. ≥ 75 years) and number of prior therapies (2 or 3 versus ≥ 3) according to IRT.
b. Log-rank test, stratified by age (< 75 years vs. ≥ 75 years) and number of prior therapies (2 or 3 versus ≥ 3) according to IRT.
c. Defined as increase of the score by at least 10 points compared with baseline (scale range 0-100).
d. Defined as decrease of the score by at least 10 points or at least 15 points compared with baseline (scale range 0-100).
e. Operationalized as CTCAE grade ≥ 3.
f. Data are only available for the discontinuation of all components.
g. See Section 2.4.1 for reasons.
h. The effect mainly arises from the effects of the severe AEs "febrile neutropenia" and "neutropenia".
i. 25% quantile and 95% CI.

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; IRT: Interactive Response Technology; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma 20; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

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

Mortality

Overall survival

There was no statistically significant difference between the treatment arms for the outcome "overall survival". This resulted in no hint of an added benefit of isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone. An added benefit is therefore not proven for this outcome.

This deviates from the assessment of the company, which derived an indication of an added benefit for overall survival.

Morbidity

Symptoms

The outcomes on symptoms were recorded with the disease-specific instruments EORTC QLQ-C30 and EORTC QLQ-MY20. The time to first deterioration by ≥ 10 points (scale range from 0 to 100) was considered.

Fatigue, nausea and vomiting, dyspnoea, insomnia, appetite loss, disease-related symptoms and side effects

No statistically significant differences between the treatment arms were shown for the outcomes "fatigue", "nausea and vomiting", "dyspnoea", "insomnia", "appetite loss", "disease-related symptoms" and "side effects". In each case, this resulted in no hint of an added benefit of isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone; an added benefit is therefore not proven.

This concurs with the company's assessment.

Pain

There was no statistically significant difference between the treatment arms for the outcome "pain". In each case, this resulted in no hint of an added benefit of isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone; an added benefit is therefore not proven.

This deviates from the assessment of the company, which derived a hint of an added benefit for the outcome "pain" based on the time to permanent deterioration.

Constipation

There is a statistically significant difference in favour of isatuximab + pomalidomide + dexamethasone for the outcome "constipation". For an outcome of the category of non-serious/non-severe symptoms/late complications, the present effect is no more than marginal. This resulted in no hint of an added benefit of isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone; an added benefit is therefore not proven.

This deviates from the assessment of the company, which derived a hint of an added benefit for the outcome "constipation" on the basis of the time to first deterioration.

Diarrhoea

There is a statistically significant difference to the disadvantage of isatuximab + pomalidomide + dexamethasone for the outcome "diarrhoea". For an outcome of the category of non-serious/non-severe symptoms/late complications, this effect was no more than marginal, however. This resulted in no hint of an added benefit of isatuximab + pomalidomide +

dexamethasone in comparison with pomalidomide + dexamethasone; an added benefit is therefore not proven.

This deviates from the assessment of the company, which derived a hint of lesser benefit on the basis of the time to first deterioration and a hint of an added benefit on the basis of the time to the permanent deterioration.

Health status (EQ-5D VAS)

The time to first deterioration by ≥ 15 points (scale range from 0-100) was considered for the outcome "health status" (EQ-5D VAS)". There was no statistically significant difference between the treatment arms. This resulted in no hint of an added benefit of isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone. An added benefit is therefore not proven for this outcome.

This concurs with the company's assessment.

Health-related quality of life

The outcomes on health-related quality of life were recorded with the disease-specific instruments EORTC QLQ-C30 and EORTC QLQ-MY20. The time to first deterioration by ≥ 10 points (scale range from 0-100) was considered.

Global health status, physical functioning, role functioning, cognitive functioning, social functioning, body image and future perspective

No statistically significant difference between the treatment arms was shown for the outcomes "global health status", "physical functioning", "role functioning", "cognitive functioning", "social functioning" and "future perspective". This resulted in no hint of an added benefit of isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone; an added benefit is therefore not proven.

For the outcomes "cognitive functioning", "social functioning", "body image" and "future perspective", this is consistent with the assessment of the company.

For the outcomes "global health status" and "physical functioning", this deviates from the assessment of the company, which derived a hint of an added benefit for the outcome "global health status" based on the time to permanent deterioration, and for the outcome "physical functioning" based on the time to the first improvement.

For the outcome "role functioning", this assessment deviates from the assessment of the company, which derived a hint of an added benefit based on the time to permanent deterioration.

Emotional functioning

There was no statistically significant difference between the treatment arms for the outcome "emotional functioning". However, there is an effect modification by the R-ISS stage (I or II

versus III) at study inclusion. For the patients with R-ISS stage III at study inclusion, there is a hint of lesser benefit (see Section 2.4.4).

This deviates from the assessment of the company, which considered the effect modification by R-ISS stage (I vs. II vs. III) as non-robust due to the small number of patients with R-ISS stage III with event and derived no added benefit for the total population without taking the effect modification into account.

Side effects

SAEs

There was no statistically significant difference between the treatment arms for the outcome "SAEs". This resulted in no hint of greater harm from isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone. Greater/lesser harm is therefore not proven for this outcome.

This concurs with the company's assessment.

Severe AEs (CTCAE grade ≥ 3)

There is a statistically significant difference to the disadvantage of isatuximab + pomalidomide + dexamethasone for the outcome “severe AEs (CTCAE grade ≥ 3)”. This resulted in a hint of greater harm from isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone.

This deviates from the assessment of the company, which derived an indication of lesser benefit.

Moreover, the company described an effect modification by R-ISS stage in Module 4 A; however, the company’s data are unusable because the assignment to the expressions of the R-ISS stage was not based on the baseline data.

Discontinuation due to AEs

For the outcome "discontinuation due to AEs”, no analyses are available for the operationalization adequate in the present comparison (discontinuation ≥ 1 drug component) (see Section 2.4.1). This resulted in no hint of greater or lesser harm from isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone; greater or lesser harm is therefore not proven.

This concurs with the assessment of the company insofar, as the company stated no greater or lesser harm for discontinuations due to AEs (based on the discontinuation of all drug components).

Infusion-related reactions

No usable data are available for infusion-related reactions (see Section 2.4.1 for reasons). This resulted in no hint of greater or lesser harm from isatuximab + pomalidomide + dexamethasone

in comparison with pomalidomide + dexamethasone; greater or lesser harm is therefore not proven.

The company did not consider the infusion-related reactions separately and derived an indication of lesser benefit for all outcomes of the category "safety and tolerability".

Specific AEs

The company did not consider the outcomes cited under the specific AEs separately and derived an indication of lesser benefit for all outcomes of the category "safety and tolerability". Therefore, the assessments of IQWiG are not compared with those of the company below.

Blood and lymphatic system disorders (SOC, severe AEs)

A statistically significant difference to the disadvantage of isatuximab + pomalidomide + dexamethasone was shown for the outcome "blood and lymphatic system disorders (SOC, severe AEs)". This resulted in a hint of greater harm from isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone.

It should be noted that blood and lymphatic system disorders are events that can be allocated also to the underlying disease of multiple myeloma.

Bronchitis (PT, AEs)

There is a statistically significant difference to the disadvantage of isatuximab + pomalidomide + dexamethasone for the outcome "bronchitis (PT, AEs)". This resulted in a hint of greater harm from isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone.

2.4.4 Subgroups and other effect modifiers

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

- sex (female versus male)
- age (< 65 vs. 65 to 75 vs. ≥ 75 years)
- R-ISS stage at study entry (I vs. II vs. III)

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

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

The company's dossier includes no subgroup analyses for the outcome "health status (EQ-5D VAS, responder analyses 15 points)".

According to the SAP, subgroup analyses on the characteristic "R-ISS stage at study inclusion (I vs. II vs. III)" were planned. However, in Module 4 A, the company describes having used the R-ISS stage at initial diagnosis in the subgroup analyses. However, deviating from the information in Module 4 A, subgroup analyses of the results from EORTC QLQ-C30, EORTC QLQ-MY20 and the EQ-5D VAS were based on the R-ISS stage at study entry; the analyses with the adequate response criterion (EORTC QLQ-C30 and EORTC QLQ-MY20) can therefore be used.

Subgroup results that meet these criteria are presented in Table 16.

Table 16: Subgroups (morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: isatuximab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone (multipage table)

Study outcome characteristic Subgroup	Isatuximab + pomalidomide + dexamethasone		Pomalidomide + dexamethasone		Isatuximab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone	
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI][a]	p-value[b]
ICARIA-MM						
Symptoms (first data cut-off) - time to first deterioration by ≥ 10 points[c]						
EORTC QLQ-C30 fatigue						
Age						
< 65 years	54	4.1 [2.2; 13.9] 33 (61.1)	70	2.8 [2.0; 4.7] 48 (68.6)	0.74 [0.47; 1.15]	0.178
65 to 75 years	68	1.9 [1.1; 2.3] 56 (82.4)	54	3.5 [2.1; 5.6] 32 (59.3)	1.87 [1.21; 2.90]	0.004
≥ 75 years	32	2.5 [1.1; 7.0] 25 (78.1)	29	1.2 [1.0; 2.5] 24 (82.8)	0.48 [0.27; 0.88]	0.016
Total					Interaction:	< 0.001[d]
EORTC QLQ-C30 appetite loss						
Age						
< 65 years	54	NA [4.8; NC] 21 (38.9)	70	9.3 [6.8; NC] 32 (45.7)	0.80 [0.46; 1.39]	0.422
65 to 75 years	68	4.7 [3.5; 5.8] 48 (70.6)	54	15.1 [6.0; NC] 21 (38.9)	2.34 [1.39; 3.96]	0.001
≥ 75 years	32	6.7 [3.0; NC] 19 (59.4)	29	4.4 [2.0; NC] 15 (51.7)	0.92 [0.47; 1.81]	0.809
Total					Interaction:	0.013[d]
EORTC QLQ-MY20 disease-related symptoms						
Age						
< 65 years	54	7.8 [5.0; NC] 26 (48.1)	70	NA [9.3; NC] 25 (35.7)	1.47 [0.85; 2.54]	0.170
65 to 75 years	68	8.3 [4.6; NC] 36 (52.9)	54	NA [NC; NC] 16 (29.6)	1.92 [1.06; 3.45]	0.028
≥ 75 years	32	6.7 [3.0; NC] 17 (53.1)	29	2.5 [1.2; 5.0] 19 (65.5)	0.54 [0.28; 1.04]	0.062
Total					Interaction:	0.011[d]

Table 16: Subgroups (morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: isatuximab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone (multipage table)

Study outcome characteristic Subgroup	Isatuximab + pomalidomide + dexamethasone		Pomalidomide + dexamethasone		Isatuximab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone	
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI][a]	p-value[b]
EORTC QLQ-MY20 side effects						
Age						
< 65 years	54	7.6 [3.8; NC] 26 (48.1)	70	5.6 [3.2; NC] 36 (51.4)	0.89 [0.54; 1.47]	0.641
65 to 75 years	68	7.0 [2.8; 9.5] 39 (57.4)	54	NA [6.6; NC] 18 (33.3)	2.07 [1.19; 3.63]	0.009
≥ 75 years	32	4.5 [2.0; NC] 18 (56.3)	29	5.7 [2.0; 8.4] 16 (55.2)	0.86 [0.44; 1.69]	0.663
Total					Interaction:	0.050[d, e]
Health-related quality of life (first data cut-off) - time to first deterioration by ≥ 10 points[f]						
EORTC QLQ-C30 role functioning						
Age						
< 65 years	54	3.8 [2.1; 13.0] 32 (59.3)	70	5.2 [3.8; 10.6] 39 (55.7)	1.15 [0.72; 1.84]	0.548
65 to 75 years	68	4.9 [2.3; 8.3] 43 (63.2)	54	3.0 [1.7; 4.8] 35 (64.8)	0.85 [0.55; 1.34]	0.491
≥ 75 years	32	5.2 [2.0; 12.5] 19 (59.4)	29	1.9 [1.0; 3.4] 22 (75.9)	0.41 [0.22; 0.77]	0.004
Total					Interaction:	0.047[d]
EORTC QLQ-C30 emotional functioning						
R-ISS (supplementary information)						
I	*39*	*NA [7.0; NC]* *14 (35.9)*	*31*	*15.2 [3.9; 15.2]* *14 (45.2)*	*0.78 [0.37; 1.64]*	*0.510*
II	*99*	*5.8 [3.8; 9.1]* *57 (57.6)*	*98*	*6.1 [3.1; NC]* *52 (53.1)*	*1.08 [0.74; 1.57]*	*0.686*
III	*16*	*3.8 [1.1; 8.6]* *9 (56.3)*	*24*	*NA [NC; NC]* *3 (12.5)*	*5.15 [1.38; 19.14]*	*0.007*
Total					*Interaction:*	*0.040*[d]

Table 16: Subgroups (morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: isatuximab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone (multipage table)

Study outcome characteristic Subgroup	Isatuximab + pomalidomide + dexamethasone		Pomalidomide + dexamethasone		Isatuximab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone	
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI][a]	p-value[b]
R-ISS						
I or II[e]	138	ND 71 (51.4)	129	ND 66 (51.2)	1.01 [0.72; 1.41]	0.950
III	16	3.8 [1.1; 8.6] 9 (56.3)	24	NA [NC; NC] 3 (12.5)	5.15 [1.38; 19.14]	0.007
Total					Interaction:	0.019[g]
EORTC QLQ-C30 social functioning						
Age						
< 65 years	54	3.1 [2.0; 8.5] 35 (64.8)	70	7.9 [3.8; 13.3] 37 (52.9)	1.44 [0.90; 2.29]	0.122
65 to 75 years	68	2.1 [1.4; 3.5] 51 (75.0)	54	4.0 [2.1; NC] 29 (53.7)	1.63 [1.03; 2.57]	0.035
≥ 75 years	32	5.2 [1.9; NC] 17 (53.1)	29	1.9 [1.0; 3.4] 21 (72.4)	0.47 [0.24; 0.89]	0.017
Total					Interaction:	0.004[d]
EORTC QLQ-MY20 future perspective						
Age						
< 65 years	54	NA [2.9; NC] 24 (44.4)	70	7.9 [2.8; 10.2] 38 (54.3)	0.76 [0.46; 1.27]	0.300
65 to 75 years	68	2.8 [2.1; 7.4] 45 (66.2)	54	NA [2.8; NC] 24 (44.4)	1.68 [1.02; 2.76]	0.039
≥ 75 years	32	6.9 [2.3; NC] 15 (46.9)	29	1.9 [1.0; 7.4] 18 (62.1)	0.54 [0.27; 1.08]	0.076
Total					Interaction:	0.012[d]

a. Unstratified Cox proportional hazards model with the factors treatment, subgroup characteristic and interaction between treatment and subgroup characteristic.
b. Using unstratified log-rank test.
c. Defined as increase of the score by at least 10 points compared with baseline (scale range 0-100).
d. From unstratified Cox proportional hazards model with the factors treatment, subgroup characteristic and interaction between treatment and subgroup characteristic.
e. Unrounded value: 0.0498.
f. Defined as decrease of the score by at least 10 points compared with baseline (scale range 0-100).
g: Institute's calculation: meta-analysis of the subgroup results for R-ISS stage I and II (fixed-effect model).

Table 16: Subgroups (morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: isatuximab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone (multipage table)

Study outcome characteristic Subgroup	Isatuximab + pomalidomide + dexamethasone		Pomalidomide + dexamethasone		Isatuximab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone	
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI][a]	p-value[b]
CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma 20; RCT: randomized controlled trial; R-ISS: Revised International Staging System; VAS: visual analogue scale						

The company derived no different added benefits for different subgroups. Therefore, the assessments of IQWiG are not compared with those of the company below.

Morbidity and health-related quality of life

Symptoms and health-related quality of life recorded with EORTC QLQ-C30 and EORTC QLQ-MY20, time to first deterioration by ≥ 10 points

Subgroup characteristic "age"

There was an effect modification (interaction tests: $p < 0.05$) by the characteristic "age (< 65 years versus 65 to 75 years versus ≥ 75 years) for each of the outcomes "fatigue", "appetite loss", "disease-related symptoms" and the symptoms side effects as well as the outcomes "role functioning", "social functioning" and "future perspective of the health-related quality of life".

The data situation in the subgroups is heterogeneous without a clear tendency, both with regard to the occurrence of effect modifications and the presence of statistically significant effects in the different age groups. Therefore, the results on the characteristic "age" from the subgroup analyses are not considered to be meaningfully interpretable, and consequently the total population is considered for the derivation of the added benefit (see Section 2.5.1).

Subgroup characteristic "R-ISS stage at study inclusion"

For the outcome "emotional functioning", there was an effect modification (interaction test: $p = 0.040$) by the characteristic R-ISS stage at study inclusion with the subgroups I, II and III. In the present data situation, the subgroups with homogeneous effects (R-ISS stage I and II) were aggregated with a fixed-effect model due to the identical study (see Figure 28 in Appendix D of the full dossier assessment). The interaction test between the subgroup results

by the characteristic R-ISS stage at study inclusion (aggregated subgroup from R-ISS stage I and II versus R-ISS stage III) produced a p-value of 0.019.

There was no statistically significant difference between the treatment arms for the aggregated subgroup patients with R-ISS stage I or II at study inclusion. A statistically significant difference to the disadvantage of isatuximab + pomalidomide + dexamethasone was shown for the subgroup of patients with R-ISS stage III at study inclusion. Hence, for patients with R-ISS stage I or II at study inclusion, there was no hint of an added benefit of isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone; an added benefit is therefore not proven. However, for patients with R-ISS stage III at study inclusion, there was a hint of lesser benefit of isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone.

2.5 Probability and extent of added benefit

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

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

2.5.1 Assessment of the added benefit at outcome level

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

Determination of the outcome category for outcomes on symptoms and side effects

It cannot be inferred from the dossier for the following outcome whether it is serious/severe or non-serious/non-severe. The classification for this outcome is justified.

For the specific side effect “bronchitis (PT, AEs)” it can be inferred from the information in Module 4 A that the majority of events were non-serious or non-severe (CTCAE grade < 3). The specific AE was therefore assigned to the outcome category “non-serious/non-severe side effects”.

The company did not assign the mentioned outcome to a severity category.

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

Outcome category **outcome** **effect modifier** **Subgroup**	**Isatuximab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone** **median or 25% quantile of the time to event** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	Median: 24.6 vs. 17.7 months HR: 0.76 [0.57; 1.01]; p = 0.056	Lesser benefit/added benefit not proven
Symptoms		
EORTC QLQ-C30 - time to first deterioration by ≥ 10 points		
Fatigue	Median: 2.3 vs. 2.8 months HR: 1.00 [0.76; 1.31]; p = 0.990	Lesser benefit/added benefit not proven
Nausea and vomiting	Median: NA vs. NA months HR: 0.97 [0.67; 1.39]; p = 0.851	Lesser benefit/added benefit not proven
Pain	Median: 5.6 vs. 6.1 months HR: 1.09 [0.81; 1.47]; p = 0.579	Lesser benefit/added benefit not proven
Dyspnoea	Median: 4.8 vs. 6.6 months HR: 1.10 [0.81; 1.51]; p = 0.541	Lesser benefit/added benefit not proven
Insomnia	Median: 6.6 vs. 9.7 months HR: 1.26 [0.92; 1.72]; p = 0.158	Lesser benefit/added benefit not proven
Appetite loss	Median: 5.8 vs. 10.7 months HR: 1.32 [0.96; 1.82]; p = 0.085	Lesser benefit/added benefit not proven
Constipation	Median: 8.1 vs. 4.3 months HR: 0.72 [0.53; 0.99]; p = 0.041	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[d]
Diarrhoea	Median: 13.0 vs. NA months HR: 1.51 [1.04; 2.20]; HR: 0.66 [0.45; 0.96][c]; p = 0.030	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[d]

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

Outcome category **outcome** **effect modifier** **Subgroup**	**Isatuximab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone** **median or 25% quantile of the time to event** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
EORTC QLQ-MY20 - time to first deterioration by ≥ 10 points		
Disease-related symptoms	Median: 7.9 vs. NA months HR: 1.28 [0.91; 1.79]; p = 0.153	Lesser benefit/added benefit not proven
Side effects	Median: 6.9 vs. 7.6 months HR: 1.20 [0.87; 1.65]; p = 0.261	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS) – time to first deterioration by ≥ 15 points		
EQ-5D VAS	Median: 10.5 vs. 15.1 months HR: 1.18 [0.84; 1.67]; p = 0.337	Lesser benefit/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 - time to first deterioration by ≥ 10 points		
Global health status	Median: 4.4 vs. 3.5 months HR: 0.93 [0.69; 1.25]; p = 0.624	Lesser benefit/added benefit not proven
Physical functioning	Median: 5.6 vs. 5.2 months HR: 0.94 [0.69; 1.27]; p = 0.658	Lesser benefit/added benefit not proven
Role functioning	Median: 4.4 vs. 3.8 months HR: 0.84 [0.63; 1.13]; p = 0.253	Lesser benefit/added benefit not proven
Emotional functioning		
R-ISS		
I or II	Median: ND HR: 1.01 [0.72; 1.41]; p = 0.950	Lesser benefit/added benefit not proven
III	Median: 3.8 vs. NA months HR: 5.15 [1.38; 19.14]; HR: 0.19 [0.05; 0.72][c]; p = 0.007 probability: "hint"	Outcome category: health-related quality of life $CI_u < 0.75$, risk ≥ 5% lesser benefit, extent: "major"
Cognitive functioning	Median: 5.7 vs. 6.1 months HR: 1.00 [0.74; 1.36]; p = 0.999	Lesser benefit/added benefit not proven

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

Outcome category **outcome** **effect modifier** **Subgroup**	**Isatuximab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone** **median or 25% quantile of the time to event** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Social functioning	Median: 2.9 vs. 4.7 months HR: 1.22 [0.91; 1.63]; p = 0.174	Lesser benefit/added benefit not proven
EORTC QLQ-MY20 - time to first deterioration by ≥ 10 points		
Body image	Median: 12.1 vs. 13.9 months HR: 1.14 [0.80; 1.62]; p = 0.457	Lesser benefit/added benefit not proven
Future perspective	Median: 5.5 vs. 6.6 months HR: 1.01 [0.74; 1.37]; p = 0.960	Lesser benefit/added benefit not proven
Side effects		
SAEs	Median: 6.0 vs. 6.6 months HR: 1.27 [0.96; 1.68]; p = 0.097	Greater/lesser harm not proven
Severe AEs	Median: 0.9 vs. 1.6 months HR: 1.50 [1.17; 1.94]; HR: 0.67 [0.52; 0.86][c]; p = 0.002 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: “considerable”
Discontinuation due to AEs	No usable results	Greater/lesser harm not proven
Infusion-related reactions	No usable data available	Greater/lesser harm not proven
Blood and lymphatic system disorders (severe AEs)	25% quantile: 0.7. vs. 1.0 months HR: 1.68 [1.22; 2.31]; HR: 0.60 [0.43; 0.82][c]; p = 0.001 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: “considerable”
Bronchitis (AEs)	25% quantile: 12.5 vs. NA months HR: 2.43 [1.38; 4.28]; HR: 0.41 [0.23; 0.72][c]; p = 0.002 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: “considerable”

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
d. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.

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

Outcome category **outcome** **effect modifier** **Subgroup**	**Isatuximab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone** **median or 25% quantile of the time to event** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; NA: not achieved; ND: no data; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma 20; R-ISS: Revised International Staging System; SAE: serious adverse event; VAS: visual analogue scale		

2.5.2 Overall conclusion on added benefit

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

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

Positive effects	**Negative effects**
–	Health-related quality of life ▪ emotional functioning ▫ R-ISS stage III hint of lesser harm – extent "major"
–	Serious/severe side effects ▪ severe AEs: hint of greater harm - extent: “considerable” ▫ specific AEs: - blood and lymphatic system disorders: hint of greater harm – extent: "considerable"
–	Non-serious/non-severe side effects ▪ specific AEs: ▫ bronchitis: hint of greater harm – extent: "considerable"
Data on the outcomes “discontinuation due to AEs (≥ 1 drug component)” and “infusion-related reactions” as well as data on the second data cut-off for the outcomes on morbidity and health-related quality of life are lacking	
AEs: adverse events; R-ISS: Revised International Staging System	

In the present data situation (barely not statistically significant effect in overall survival, final data cut-off still pending), an added benefit of isatuximab + pomalidomide + dexamethasone over pomalidomide + dexamethasone is not proven for adults with relapsed and refractory multiple myeloma who have received ≥ 2 prior therapies, including lenalidomide and a proteasome inhibitor, and who showed disease progression under the last therapy.

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

Table 19: Isatuximab + pomalidomide + dexamethasone – probability and extent of added benefit:

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with relapsed and refractory multiple myeloma who have received ≥ 2 prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression under the last therapy[b]	▪ Bortezomib in combination with dexamethasone, or ▪ lenalidomide in combination with dexamethasone, or ▪ **pomalidomide in combination with dexamethasone**, or ▪ elotuzumab in combination with lenalidomide and dexamethasone, or ▪ elotuzumab in combination with pomalidomide and dexamethasone, or ▪ carfilzomib in combination with lenalidomide and dexamethasone, or ▪ carfilzomib in combination with dexamethasone, or ▪ daratumumab in combination with lenalidomide and dexamethasone, or ▪ daratumumab in combination with bortezomib and dexamethasone	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. It is assumed that high-dose chemotherapy with stem cell transplantation is not an option for the patients at the time point of their current treatment.

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

The assessment described above deviates from that of the company, which derived an indication of considerable added benefit for all patients of the target population.

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

References for English extract

Please see full dossier assessment for full reference list.

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

1. Institute for Quality and Efficiency in Health Care. General Methods; Version 6.0 [online]. 2020 [Accessed: 22.03.2021]. URL: https://www.iqwig.de/methoden/general-methods_version-6-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

3. Sanofi. A Phase 3 randomized, open-label, multicenter study comparing isatuximab (SAR650984) in combination with pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with refractory or relapsed and refractory multiple myeloma; study EFC14335; Clinical Study Report [unpublished]. 2021.

4. Sanofi. Multinational Clinical Study Comparing Isatuximab, Pomalidomide, and Dexamethasone to Pomalidomide and Dexamethasone in Refractory or Relapsed and Refractory Multiple Myeloma Patients (ICARIA-MM) [online]. 2021 [Accessed: 18.06.2021]. URL: https://ClinicalTrials.gov/show/NCT02990338.

5. Sanofi-aventis recherche & développement. A Phase 3 Randomized, Open-label, Multicenter Study Comparing Isatuximab (SAR650984) in Combination with Pomalidomide and Low-dose Dexamethasone versus Pomalidomide and Low-dose Dexamethasone in Patients with Refractory or Relapsed and Refractory Multiple Myeloma [online]. [Accessed: 18.06.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-003097-41.

6. Attal M, Richardson PG, Rajkumar SV et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. Lancet 2019; 394(10214): 2096-2107. https://dx.doi.org/10.1016/S0140-6736(19)32556-5.

7. European Mediciens Agency. Sarclisa; Assessment report [online]. 2020 [Accessed: 17.05.2021]. URL: https://www.ema.europa.eu/documents/assessment-report/sarclisa-epar-public-assessment-report_en-0.pdf.

8. Dimopoulos MA, Leleu X, Moreau P et al. Isatuximab plus pomalidomide and dexamethasone in relapsed/refractory multiple myeloma patients with renal impairment: ICARIA-MM subgroup analysis. Leukemia 2021; 35(2): 562-572. https://dx.doi.org/10.1038/s41375-020-0868-z.

9. Kumar S, Paiva B, Anderson KC et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol 2016; 17(8): e328-e346. https://dx.doi.org/10.1016/s1470-2045(16)30206-6.

10. Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie. Multiples Myelom [online]. 2018 [Accessed: 21.05.2021]. URL: https://www.onkopedia.com/de/onkopedia/guidelines/multiples-myelom/@@pdf-latest?filename=multiples-myelom.pdf.

11. Dimopoulos MA, Moreau P, Terpos E et al. Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Ann Oncol 2021; 32(3): 309-322. https://dx.doi.org/10.1016/j.annonc.2020.11.014.

12. Celgene. IMNOVID Hartkapseln [online]. 2020 [Accessed: 23.06.2021]. URL: https://www.fachinfo.de/.

13. Sanofi. SARCLISA 20 mg/ml Konzentrat zur Herstellung einer Infusionslösung [online]. 2021 [Accessed: 23.06.2021]. URL: https://www.fachinfo.de.

14. Bundesinstitut für Arzneimittel und Medizinprodukte. Zulassungen für Humanarzneimittel mit dem Wirkstoff „Ranitidin“: Ruhen der Zulassung von Arzneimitteln; EMEA/H/A-31/1491 [online]. 2021 [Accessed: 05.07.2021]. URL: https://www.bfarm.de/SharedDocs/Downloads/DE/Arzneimittel/Pharmakovigilanz/Risikoinformationen/RisikoBewVerf/m-r/ranitidin_bescheid_20210107.pdf;jsessionid=673D08E7CF9B1F4E98B50E4F17DA57EA.intranet662?__blob=publicationFile.

15. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Dokumentation und Würdigung der Anhörung zum Entwurf der Allgemeinen Methoden 6.0 [online]. 2020 [Accessed: 27.01.2021]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_dwa-entwurf-fuer-version-6-0_v1-0.pdf.

16. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Atezolizumab (hepatozelluläres Karzinom) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2021 [Accessed: 01.03.2021]. URL: https://www.iqwig.de/download/a20-97_atezolizumab_nutzenbewertung-35a-sgb-v_v1-0.pdf.

17. Gemeinsamer Bundesausschuss. Antworten auf häufig gestellte Fragen zum Verfahren der Nutzenbewertung [online]. [Accessed: 17.06.2021]. URL: https://www.g-ba.de/themen/arzneimittel/arzneimittel-richtlinie-anlagen/nutzenbewertung-35a/faqs/#wie-soll-vor-dem-hintergrund-der-veroffentlichung-des-methodenpapiers-60-des-iqwig-am-5-november-2020-derzeit-in-der-dossiererstellung-mit-der-bestimmung-von-klinischen-relevanzschwellen-bei-komplexen-skalen-umgegangen-werden.

18. Food and Drug Administration. BLA Multi-disciplinary Review and Evaluation BLA 761113: Sarclisa (isatuximab) [online]. 2020 [Accessed: 18.06.2021]. URL: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/761113Orig1s000MultidisciplineR.pdf.

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