IQWiG Reports – Commission No. A21-90

Elotuzumab (multiple myeloma) –

Benefit assessment according to §35a Social Code Book V[1] (expiry of the decision)

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Elotuzumab (multiples Myelom) – Nutzenbewertung gemäß § 35a SGB V (Ablauf Befristung)* (Version 1.0; Status: 29 September 2021). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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[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
CTCAE	Common Terminology Criteria for Adverse Events
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EQ-5D VAS	European Quality of Life Questionnaire – 5 Dimensions visual analogue scale
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
ISS	International Staging System
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MDASI-MM	M. D. Anderson Symptom Inventory – Multiple Myeloma Module
PFS	progression-free survival
PT	preferred term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

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 elotuzumab (in combination with pomalidomide and dexamethasone). The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 1 July 2021.

The present assessment is a reassessment after expiry of the decision time limit. The G-BA has imposed a time limit on its decision regarding the previous assessment because the submitted dossier was based on an interim analysis of the ELOQUENT-3 study. The imposed time limit was contingent upon the submission of the results of the final analysis for all outcomes used in the benefit assessment.

Research question

The aim of this report is to assess the added benefit of elotuzumab in combination with pomalidomide and dexamethasone in comparison with the appropriate comparator therapy (ACT) in adult patients with relapsed and refractory multiple myeloma who have received at least 2 prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the most recent therapy.

The G-BA's ACT is presented in Table 2.

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

Therapeutic indication	**ACT**[a]
Treatment of adult patients with relapsed and refractory multiple myeloma who have received at least 2 prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on 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 ▪ Carfilzomib in combination with lenalidomide and dexamethasone or ▪ Carfilzomib in combination with dexamethasone or ▪ Daratumumab in combination with lenalidomide and dexamethasone or ▪ Daratumumab in combination with bortezomib and dexamethasone
a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is marked in **bold**. b. High-dose chemotherapy with stem cell transplantation is assumed not to be an option for patients at the time of the current therapy. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA's specification of the ACT. From the stated options, the company selected pomalidomide in combination with dexamethasone.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier.

Study pool and study design

The added benefit of elotuzumab was assessed using the ELOQUENT-3 (CA204-125) study.

The ELOQUENT-3 study is a randomized controlled trial (RCT) comparing a triple combination of elotuzumab, pomalidomide, and dexamethasone with the dual combination of pomalidomide and dexamethasone. The study investigated adult patients with relapsed and refractory multiple myeloma who had received at least 2 prior lines of therapy. Patients had to have relapsed after treatment with lenalidomide or a proteasome inhibitor, or be refractory to at least one of these drugs. In addition, they had to be refractory to their most recent prior therapy.

Based on the treatment algorithm presented in the guidelines, it is safe to assume that, in the given therapeutic indication, patients without prior stem cell transplantation were not indicated for high-dose chemotherapy with subsequent stem cell transplantation.

The study included a total of 117 randomized patients. Neither patients nor study staff were blinded to treatment. Patients were stratified by the number of prior lines of therapy (2 to 3 versus ≥ 4) and International Staging System (ISS) stage at baseline (I to II versus III). Switching from the comparator therapy (pomalidomide + dexamethasone) to the intervention therapy (triple combination of elotuzumab + pomalidomide + dexamethasone) was disallowed.

The dosing and administration schedule for the study medication is in accordance with the respective Summaries of Product Information (SPC).

The primary outcome was progression-free survival (PFS); surveyed patient-relevant secondary outcomes were overall survival, symptoms, health status, and adverse events (AEs).

A total of 3 data cut-offs are available for the study: The first data cut-off from 21 February 2018 was predefined and performed after a specific number of progression events. The second data cut-off from 29 November 2018 had been requested by the European Medicines Agency (EMA) during the approval process and formed the basis for the first assessment of elotuzumab (in combination with pomalidomide and dexamethasone). The third data cut-off was implemented, as predefined, after 78 deaths, which was on 22 February 2021. At the time of the previous benefit assessment, the third data cut-off had not yet occurred. According to the study protocol, this cut-off will be the basis for the final analysis of overall survival. The third data cut-off forms the basis for the present benefit assessment. Results on all relevant outcomes were available for this data cut-off.

Risk of bias

The results for all relevant outcomes except overall survival are potentially highly biased. The reasons for this bias vary by outcome:

The risk of bias regarding the results for the outcomes of health status and symptoms is high because, firstly, the questionnaires survey patients' subjective opinions. Secondly, return rates differ between study arms and decrease over the course of the study.

For the outcomes of serious AEs (SAEs) and severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3), the risk of bias of results is deemed high due to potentially informative censoring. For the outcome of discontinuation due to AEs (≥ 1 drug component), lack of blinding in the presence of a subjective decision on treatment discontinuation is deemed to lead to high risk of bias.

All in all, it is possible to derive at most an indication, e.g. of added benefit, for the outcome of overall survival and a hint for all other relevant outcomes.

Results

Mortality

Overall survival

For the outcome of overall survival, there is an effect modification by the attribute of prior stem cell therapy (yes/no).

For patients without prior stem cell therapy, there is a statistically significant effect in favour of elotuzumab + pomalidomide + dexamethasone. This results in an indication of added benefit in comparison with the ACT.

No statistically significant difference between treatment groups was found for patients with prior stem cell transplantation. Consequently, there is no hint of added benefit of elotuzumab + pomalidomide + dexamethasone in comparison with the ACT; an added benefit is therefore not proven.

Morbidity

Health status

For the outcome of health status, as surveyed using the European Quality of Life Questionnaire – 5 Dimensions visual analogue scale (EQ-5D VAS), there was no statistically significant difference between treatment groups. This results in no hint of added benefit of elotuzumab + pomalidomide + dexamethasone in comparison with the ACT; an added benefit is therefore not proven.

Symptoms

Outcomes regarding symptoms were surveyed using the M. D. Anderson Symptom Inventory – Multiple Myeloma Module (MDASI-MM).

Symptom severity (MDASI-MM, Total Symptom Severity Score)

For the outcome of symptom severity, no statistically significant difference between treatment groups was found. This results in no hint of added benefit of elotuzumab + pomalidomide + dexamethasone in comparison with the ACT; an added benefit is therefore not proven.

Symptom interference with daily life (MDASI-MM Symptom Interference Score)

For the outcome of symptom interference with daily life, no statistically significant difference between treatment groups was found. This results in no hint of added benefit of elotuzumab + pomalidomide + dexamethasone in comparison with the ACT; an added benefit is therefore not proven.

Health-related quality of life

The outcome of health-related quality of life was not surveyed by the ELOQUENT-3 study.

Side effects

SAEs

For the outcome of SAEs, no statistically significant difference between treatment groups was found. This results in no hint of greater or lesser harm from elotuzumab + pomalidomide + dexamethasone in comparison with the ACT; greater or lesser harm is therefore not proven.

Severe AEs (CTCAE grade ≥ 3)

For the outcome of severe AEs (CTCAE grade ≥ 3), there is an effect modification by the attribute of prior lines of therapy.

For patients with 2 or 3 prior lines of therapy, there is a statistically significant effect in favour of elotuzumab + pomalidomide + dexamethasone. This results in a hint of lesser harm in comparison with the ACT.

No statistically significant difference between treatment groups was found for patients with 4 or more prior lines of therapy. This results in no hint of greater or lesser harm from elotuzumab + pomalidomide + dexamethasone in comparison with the ACT; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

For the outcome of discontinuation due to AEs, no statistically significant difference between treatment groups was found. This results in no hint of greater or lesser harm from elotuzumab + pomalidomide + dexamethasone in comparison with the ACT; greater or lesser harm is therefore not proven.

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

On the basis of the presented results, the probability and extent of added benefit of the drug elotuzumab (in combination with pomalidomide and dexamethasone) in comparison with the ACT are assessed as follows:

Overall, exclusively favourable effects of different certainties of results (indication or hint) were found for elotuzumab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone in the outcome categories of mortality and side effects, each of them applying only to subpopulations.

[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].

Regarding the outcome of overall survival, an indication of major added benefit was found for patients without prior stem cell therapy. In addition, there is a hint of lesser harm regarding the outcome of severe AEs (CTCAE grade ≥ 3) for patients with 2 to 3 prior lines of therapy.

Taking into account both effect modifications for the 2 outcomes, no meaningful summary interpretation of results can be derived from the available information. Due to the fatal course of disease, the outcome overall survival is attributed greater relevance in this situation; therefore, this outcome is considered a priority. Consequently, for the overall conclusion on added benefit, only the attribute of prior stem cell transplantation (yes/no) is used due to the effect modification for the outcome overall survival.

In summary, there is an indication of major added benefit of elotuzumab + pomalidomide + dexamethasone in comparison with the ACT for adult patients with relapsed and refractory multiple myeloma who have received at least 2 prior therapies including lenalidomide and a proteasome inhibitor, have demonstrated disease progression on the most recent therapy, and received no prior stem cell therapy. No added benefit has been proven for patients who received prior stem cell therapy.

Table 3: Elotuzumab + pomalidomide + dexamethasone – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Treatment of adult patients with relapsed and refractory multiple myeloma who have received at least 2 prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on 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 ▪ 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	Patients **without** prior stem cell therapy: ▪ Indication of major added benefit
		Patients **with** prior stem cell therapy: ▪ Added benefit not proven

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is marked in **bold**.
b. High-dose chemotherapy with stem cell transplantation is assumed not to be an option for patients at the time of the current therapy.

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

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

Supplementary note on the ACT

After dossier submission, the G-BA modified the ACT by including bortezomib in combination with pegylated liposomal doxorubicin as an additional option for the ACT. The present benefit assessment is based on the originally specified ACT. Implementation of the modified ACT would not affect the relevance of the data used in this benefit assessment.

2.2 Research question

The aim of this report is to assess the added benefit of elotuzumab in combination with pomalidomide and dexamethasone (hereinafter referred to as "elotuzumab + pomalidomide + dexamethasone") in comparison with the ACT in adult patients with relapsed and refractory multiple myeloma who have received at least 2 prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the most recent therapy.

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

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

Therapeutic indication	**ACT**[a]
Treatment of adult patients with relapsed and refractory multiple myeloma who have received at least 2 prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on 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 ▪ Carfilzomib in combination with lenalidomide and dexamethasone or ▪ Carfilzomib in combination with dexamethasone or ▪ Daratumumab in combination with lenalidomide and dexamethasone or ▪ Daratumumab in combination with bortezomib and dexamethasone
a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is marked in **bold**. b. High-dose chemotherapy with stem cell transplantation is assumed not to be an option for patients at the time of the current therapy. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA's specification of the ACT. From the stated options, the company selected pomalidomide in combination with dexamethasone (hereinafter referred to as "pomalidomide + dexamethasone").

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier.

2.3 Information retrieval and study pool

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

Sources cited by the company in the dossier:

- Study list on elotuzumab (as of 5 April 2021)
- Bibliographic literature search on elotuzumab (most recent search on 6 April 2021)
- Search in trial registries / study results databases on elotuzumab (most recent search on 5 April 2021)
- Search on the G-BA website on elotuzumab (most recent search on 5 April 2021)

To check the completeness of the study pool:

- Search in trial registries for studies on elotuzumab (most recent search on 9 July 2021); see Appendix A of the full dossier assessment for search strategies.

The check did not identify any additional relevant studies.

2.3.1 Included studies

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

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

Study	Study category			Available sources		
	Approval study for the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (yes/no [reference])	Registry entries[b] (yes/no [reference])	Publication and other sources[c] (yes/no [reference])
CA204-125 (ELOQUENT-3[d])	Yes	Yes	No	Yes [3-7]	Yes [8-12]	Yes [13-18]

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the tables below, the study will be referred to by this acronym.

G-BA: Federal Joint Committee; RCT: randomized controlled trial

The study pool is consistent with that selected by the company. The ELOQUENT-3 study has already been used as the basis for the previous benefit assessment of elotuzumab + pomalidomide + dexamethasone in this therapeutic indication [17,18] The present benefit assessment is based on the final analysis of the ELOQUENT-3 study.

2.3.2 Study characteristics

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

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and time period conducted	Primary outcome; secondary outcomes[a]
ELOQUENT-3	RCT, open-label, parallel-group	Patients ≥ 18 years of age with relapsed and refractory multiple myeloma ▪ with ≥ 2 prior lines of therapy, including ≥ 2 consecutive cycles of lenalidomide and/or a proteasome inhibitor ▪ ECOG-PS ≤ 2	Elotuzumab + pomalidomide + dexamethasone (N = 60) Pomalidomide + dexamethasone (N = 57)	Screening: maximum of 28 days Treatment: in 28-day cycles until disease progression, unacceptable toxicity, withdrawal of consent, study termination by the sponsor, start of another anti-myeloma treatment Follow-up observation[b]: outcome-specific, maximally until death, discontinuation of study participation, or study termination by the sponsor	A total of 39 sites in Canada, France, Germany, Greece, Italy, Japan, Netherlands, Poland, Spain, United States 03/2016–ongoing 1st data cut-off: 21/02/2018 2nd data cut-off: 29/11/2018 3rd data cut-off (final data cut-off): 22/02/2021	Primary: progression-free survival Secondary: overall survival, symptoms, health status, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. Outcome-specific data are provided in Table 8.

AE: adverse event; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; N: number of randomized (included) patients; RCT: randomized controlled trial

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

Study	Intervention	Comparison
ELOQUENT-3	Elotuzumab: ▪ Cycles[a] 1 + 2: 10 mg/kg i.v. on Days 1, 8, 15, and 22 ▪ From Cycle 3: 20 mg/kg i.v. on Day 1 Pomalidomide: ▪ 4 mg orally once daily, on Days 1–21 of a cycle ▪ Dose interruption in case of thrombocytopoenia and neutropoenia; in case of normalization, continued treatment with 3 mg; in case of further deterioration, reduction by another 1 mg Dexamethasone[b]: ▪ Cycles 1 + 2: on Days 1, 8, 15, 22 ▫ ≤ 75 years old: 28 mg p.o. + 8 mg i.v. ▫ > 75 years old: 8 mg p.o. + 8 mg i.v.[c] ▪ Cycle 3 and beyond: on Days 1, 8, 15, 22 ▫ ≤ 75 years old: Day 1: 28 mg p.o. + 8 mg i.v.; Days 8, 15, 22: 40 mg p.o. ▫ > 75 years old: Day 1: 8 mg p.o. + 8 mg i.v.[c]; Days 8, 15, 22: 20 mg p.o. Dose reduction/interruption depending on the observed side effect[d]	Pomalidomide: ▪ 4 mg p.o. once daily, on Days 1–21 of a cycle[a] ▪ Dose interruption in case of thrombocytopoenia and neutropoenia; in case of normalization, continued treatment with 3 mg; in case of further deterioration, reduction by another 1 mg Dexamethasone: ▪ ≤ 75 years old: 40 mg p.o. on Days 1, 8, 15, 22 of all cycles ▪ > 75 years old: 20 mg p.o. on Days 1, 8, 15, 22 of all cycles Dose reduction depending on the observed side effect
	Discontinuation of 1 component of the study medication does not necessarily lead to the discontinuation of all drugs; continuing treatment with individual components or a dual combination is permissible.	
	Premedication before elotuzumab: ▪ H1 and H2 blockers (e.g. diphenhydramine or ranitidine), paracetamol **Nonpermitted prior treatment:** ▪ Autologous stem cell therapy within 12 weeks of treatment start ▪ Allogeneic stem cell therapy within 12 months of treatment start ▪ Pomalidomide ▪ Melphalan or monoclonal antibodies within 6 weeks of treatment start **Concomitant treatment** <u>Obligatory</u>: ▪ Thrombosis prevention (e.g. acetylsalicylic acid, low-molecular-weight heparin, vitamin K antagonist) <u>As needed:</u> ▪ Treatment of infusion-related reactions (e.g. i.v. corticosteroids, H2 inhibitors, leukotriene inhibitors), oxygen inhalation, epinephrine, bronchodilators, oral antiviral and antimicrobial prophylaxis, antiemetics, bisphosphonates, erythropoietin, G-CSF for neutropoenia <u>Disallowed:</u> ▪ Other anti-myeloma treatments within 14 days before treatment start ▪ Steroids other than dexamethasone, low-dose prednisone or steroids with low systemic absorption ▪ Other experimental therapies	

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

Study	Intervention	Comparison
a. In both study arms, treatment was administered in 28-day cycles. b. In case of infusion-related reactions to elotuzumab administration, the intravenous dexamethasone component is increased depending on the severity of the reaction, and the oral dose is reduced accordingly to achieve a stable total dose. In case of prior grade 2 infusion reaction, dexamethasone was administered in the form of 10 mg i.v. and 28 mg p.o.; in case of grade 3 or repeated grade 2 reaction, 18 mg i.v. and 2 doses of 8 mg p.o. were administered. In patients ≥ 75 years of age, the same regimen was used at lower doses. c. In case of omission or late administration of the elotuzumab dose, dexamethasone is to be administered p.o. as in the comparator arm. d. For dexamethasone, a dose reduction is possible only for the p.o. dose, while the i.v. dose is always 8 mg. G-CSF: granulocyte colony-stimulating factor; H: histamine; i.v.: intravenously; p.o.: orally; RCT: randomized controlled trial		

The ELOQUENT-3 study is an RCT comparing a triple combination of elotuzumab, pomalidomide, and dexamethasone with the dual combination of pomalidomide and dexamethasone. It is a phase II study which serves as the basis for elotuzumab approval in the present therapeutic indication. The study investigated adult patients with relapsed and refractory multiple myeloma who had received at least 2 prior lines of therapy. Patients had to have relapsed after treatment with lenalidomide or a proteasome inhibitor, or be refractory to at least one of these drugs. In addition, they had to be refractory to their most recent prior therapy.

The European Public Assessment Report (EPAR) of the EMA indicates that the therapeutic indication stated in the approval, relapsed and refractory multiple myeloma , pertains to the situation in the ELOQUENT-3 approval study [19]. Thus, consistent with the approval study's inclusion criteria, the terms relapsed and refractory multiple myeloma cover the following requirements for response to or failure of prior therapies, as applicable:

- Refractory to the most recent prior therapy for multiple myeloma (irrespective of drug or drug combination) and
- Refractory to prior lenalidomide and/or proteasome inhibitor treatment or
- If lenalidomide or proteasome inhibitors do not represent the most recent line of therapy: partial response to at least one line of therapy with these drugs before the relapse

Both the approval study and treatment recommendations define refractory disease as disease progression on treatment or within 60 days thereafter. Relapse is defined as disease progression after response to treatment within 6 months [20].

Patients with prior pomalidomide treatment were not allowed to participate in the ELOQUENT-3 study. This rules out an unsuitability of pomalidomide for the participating patients due to refractoriness. Nor are any other reasons apparent that would prevent the suitability of pomalidomide. Autologous stem cell transplantation within 12 weeks before enrolment and

allogeneic stem cell transplantation within 12 months before enrolment were also excluded. However, based on the treatment algorithm presented in the guidelines, it is safe to assume that, in the present therapeutic indication, patients without prior stem cell transplantation were not indicated for high-dose chemotherapy with subsequent stem cell transplantation at enrolment [20,21].

The study included a total of 117 randomized patients. Neither patients nor study staff were blinded to treatment. Patients were stratified by the number of prior lines of therapy (2 to 3 versus ≥ 4) and International Staging System (ISS) stage at baseline (I to II versus III). Switching from the comparator therapy (pomalidomide + dexamethasone) to the intervention therapy (triple combination of elotuzumab + pomalidomide + dexamethasone) was disallowed.

The dosing and administration schedule for the study medication is in accordance with the respective SPCs [22,23].

The primary outcome is PFS. Surveyed patient-relevant secondary outcomes are overall survival, symptoms, health status, and AEs.

A total of 3 data cut-offs are available for the study: The first data cut-off from 21 February 2018 was predefined and performed after a specific number of progression events. A study report is available on this data cut-off. The second data cut-off was requested by the EMA during the approval process in order to obtain current data on overall survival; said cut-off occurred on 29 November 2018. The third data cut-off was implemented, as predefined, after 78 deaths, which was on 22 February 2021. At the time of the previous benefit assessment, the third data cut-off had not yet occurred. According to the study protocol, this cut-off will be the basis for the final analysis of overall survival. The third data cut-off forms the basis for the present benefit assessment. For this data cut-off, results are available on all relevant outcomes.

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

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

Study **Outcome category** **Outcome**	**Planned follow-up observation**
ELOQUENT-3	
Mortality	
Overall survival	After treatment end until death, study end, or withdrawal of consent
Morbidity	
Health status (EQ-5D VAS), symptoms (MDASI-MM	After treatment end until death, study end, or withdrawal of consent[a]
Health-related quality of life	Not surveyed in the study[b]
Side effects	
Outcomes of the side effects category	Until 60 days after treatment end[c]

a. Outcomes might have been surveyed only until treatment discontinuation.
b. The company allocated the MDASI-MM subscales of Activity Interference, Affective Interference, and Symptom Interference to the outcome category of health-related quality of life (see Section 2.4.1).
c. The company reports that additional primary tumours were surveyed beyond this time period.

EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; MDASI-MM: M. D. Anderson Symptom Inventory – Multiple Myeloma Module; RCT: randomized controlled trial; VAS: visual analogue scale

Having been recorded only for the period of treatment with the study medication (plus 60 days), the follow-up durations for side effects outcomes (except for additional primary tumours) were systematically shortened. To be able to draw a reliable conclusion for the entire study period or until patient death, these outcomes, similar to survival, would have to be surveyed and analysed over the entire period.

For the outcomes of health status and symptoms, follow-up was supposed to be continued beyond treatment discontinuation, for the entire study participation period. However, it cannot be ruled out that, contrary to the information provided in the study documents, these outcomes were recorded only until treatment discontinuation. As described in the previous assessment A19-80 [17], questionnaire return rates differ between treatment arms and decrease in the course of the study. This observation continues to be true for the final data cut-off. The company did not provide any reasons for the missing questionnaires. According to the dossier, the follow-up of outcomes was to be continued after the end of treatment, until death, end of study, or withdrawal of consent. The missing values are not exclusively due to patient death. Instead, the decreasing return rates clearly align with PFS events over time; this raises the question whether, contrary to the study protocol, outcome follow-up was discontinued or no longer systematically continued after the end of treatment,

Table 9 shows the patient characteristics of the included study.

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

Study Characteristics Category	**Elotuzumab + pomalidomide + dexamethasone N[a] = 60**	**Pomalidomide + dexamethasone N[a] = 57**
ELOQUENT-3		
Age [years], mean (SD)	66 (10)	66 (10)
Sex [f/m], %	47/53	39/61
Ancestry, n (%)		
White	45 (75.0)	45 (78.9)
Black / African American	0 (0.0)	1 (1.8)
Asian	15 (25.0)	9 (15.8)
Other	0 (0.0)	2 (3.5)
ECOG PS		
0	28 (46.7)	23 (40.4)
1	28 (46.7)	26 (45.6)
2	4 (6.7)	8 (14.0)
ISS stage at baseline, n (%)		
I	32 (53.3)	27 (47.4)
II	21 (35.0)	23 (40.4)
III	7 (11.7)	7 (12.3)
Disease duration: time between first diagnosis and randomization [months], median (Q1; Q3)	57.7 (29.0; 94.2)	53.1 (34.4; 79.3)
Cytogenetic risk group, n (%)		
High risk	4 (6.7)	7 (12.3)
Low risk	2 (3.3)	1 (1.8)
Standard risk	44 (73.3)	40 (70.2)
Undetermined	10 (16.7)	9 (15.8)
Type of myeloma, n (%)		
IgG	35 (58.3)	25 (43.9)
IgA	11 (18.3)	14 (24.6)
IgM	0 (0.0)	0 (0.0)
Light chain disease	12 (20.0)	17 (29.8)
Biclonal myeloma	1 (1.7)	1 (1.8)
Triclonal myeloma	0 (0.0)	0 (0.0)
Not classified	1 (1.7)	0 (0.0)
Number of prior lines of treatment, n (%)		
1	0 (0.0)	0 (0.0)
2	14 (23.3)[b]	18 (31.6)
3	21 (35.0)[b]	18 (31.6)
≥ 4	25 (41.7)	21 (36.8)

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

Study Characteristics Category	**Elotuzumab + pomalidomide + dexamethasone N[a] = 60**	**Pomalidomide + dexamethasone N[a] = 57**
Refractory[c], n (%)		
to lenalidomide	54 (90.0)	48 (84.2)[b]
to proteasome inhibitors	47 (78.3)	47 (82.5)
to bortezomib	38 (63.3)	38 (66.7)
to carfilzomib	9 (15.0)	15 (26.3)
to ixazomib	5 (8.3)	2 (3.5)
to lenalidomide and proteasome inhibitors	41 (68.3)	41 (71.9)
Relapsed[c], n (%)		
after lenalidomide	5 (8.3)[b]	7 (12.3)[b]
after proteasome inhibitors	13 (21.7)	8 (14.0)
after bortezomib	17 (28.3)	10 (17.5)[b]
after carfilzomib	0 (0.0)	1 (1.8)
after ixazomib	0 (0.0)	0 (0.0)
after lenalidomide and proteasome inhibitors	0 (0.0)	3 (5.3)[b]
Refractory to lenalidomide and relapsed after proteasome inhibitor or vice versa	18 (30.0)[b]	9 (15.8)[b]
Further prior therapies		
Stem cell transplantation	31 (51.7)	33 (57.9)
Radiotherapy	14 (23.3)	12 (21.1)
Surgery	8 (13.3)	10 (17.5)
Treatment discontinuation, n (%)	58 (96.7[d])	54 (94.7[d])
Study discontinuation, n (%)	ND	ND

a. Number of randomized patients. Values which are based on different patient numbers are marked in the corresponding line, provided the deviation is relevant.
b. Discrepancy between Module 4 B and Module 5 of the dossier. The information provided in the table is from Module 5. The corresponding information from Module 4 B is found in Table 4-11 included therein.
c. According to inclusion criteria, all included patients were refractory to the most recent prior therapy. See Section 2.3.2 for definitions of refractory and relapsed disease.
d. IQWiG calculations.

ECOG-PS: Eastern Cooperative Oncology Group Performance Stastus; f: female; Ig: immunoglobulin; ISS: International Staging System; m: male; n: number of patients in the category; N: number of randomized (or included) patients; ND: no data; Q1: 1st quartile; Q3: 3rd quartile; RCT: randomized controlled trial; SD: standard deviation

The patient population of the ELOQUENT-3 study shows slight differences between treatment groups for some patient characteristics, e.g., sex, ECOG-PS, ISS stage at baseline, cytogenetic risk group, number of prior lines of therapy, and prior stem cell therapies. This is probably due to the small study population; it is safe to assume that these differences have no relevant influence on the interpretation of the study results.

The mean age of the patients was 66 years. There were slightly more men than women. The majority of patients (> 75%) were white or of European origin; the others were mainly from the Asian region, with a higher proportion found in the intervention arm. The patients' general condition was mostly good (about 90% with Eastern Cooperative Oncology Group Performance Status [ECOG PS] ≤ 1). The intervention arm included slightly more patients with an ECOG-PS of 0, while the comparator arm had slightly more patients with an ECOG-PS of 2. Disease severity according to ISS stage was low in about half of the patients (stage I). Just under 52% and 58%, respectively, of the patients had been treated with stem cell transplantation before enrolment. All patients had received at least 2 prior drug therapies before starting the study. Most patients were refractory to lenalidomide and/or at least 1 proteasome inhibitor.

Follow-up period and treatment duration in the ELOQUENT-3 study

Table 10 shows the mean and median treatment durations as well as the mean and median follow-up periods for individual outcomes.

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

Study **Duration of the study phase** **Outcome category**	**Elotuzumab + pomalidomide + dexamethasone**	**Pomalidomide + dexamethasone**
ELOQUENT-3		
Treatment duration [months]	N = 60	N = 55[a]
Median [min; max]	Elotuzumab: 7.6 [0.3; 50.5] Pomalidomide: 8.1 [< 0.1; 50.5] Dexamethasone: 8.1 [0.3; 50.5]	– Pomalidomide: 4.4 [0.3; 47.8] Dexamethasone: 4.2 [< 0.1; 39.4]
Mean (SD)	Elotuzumab: 12.3 (ND) Pomalidomide: 12.6 (ND) Dexamethasone: 12.6 (ND)	– Pomalidomide: 7.8 (ND) Dexamethasone: 6.8 (ND)
Follow-up duration [months]	N = 60	N = 57
Overall survival[b]		
Median [min; max]	26.5 [0.5; 52.0]	16.7 [0.6; 52.2]
Mean (SD)	27.1 (17.0)	21.0 (16.3)
Morbidity[c]	ND	ND
Health-related quality of life	No data available[d]	
Side effects[e]	ND	ND

a. Only patients who had received treatment were analysed regarding treatment duration.
b. The company did not provide any information on the methods used for determining follow-up durations.
c. According to the study documents, follow-up observation for the morbidity outcomes, similar to the outcome of overall survival, was to continue until death; see Table 8. Module 4 B states that the follow-up duration is the same as for overall survival.
d. The company allocated the MDASI-MM subscales of Activity Interference, Affective Interference, and Symptom Interference to the outcome category of health-related quality of life (see Section 2.4.1).
e. According to the study protocol and Module 4 B, side effects (except additional primary tumours) were recorded for 60 days after the last dose.

max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

Given that it was possible to discontinue the individual components of the study medication independently of one another, there was no uniform treatment duration. The differences in treatment duration of individual drugs within the treatment arms are small, however. It is therefore permissible to conduct meaningful comparisons of the median and mean treatment durations between the arms. The company provided specific data only on the follow-up duration for the outcome of overall survival. For AEs (except additional primary tumours), the follow-up duration is linked to the duration of therapy and ends 60 days after discontinuation of the study medication. It can therefore be inferred from the median treatment durations in the individual study arms that the follow-up duration for AEs in the comparator arm is only about 60% of the follow-up duration in the intervention arm. According to the study documents, analogous to overall survival, all other patient-relevant outcomes are to be followed up until death, but the company did not report their specific follow-up durations.

Subsequent therapies

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

Table 11: Subsequent systemic therapies – RCT, direct comparison: elotuzumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone (multipage table)

Study Drug	Patients with subsequent therapy n (%)[a]	
	Elotuzumab + pomalidomide + dexamethasone N = 60	Pomalidomide + dexamethasone N = 57
ELOQUENT-3		
Total	42 (70.0)	39 (68.4)
Dexamethasone	37 (61.7)	37 (64.9)
Daratumumab	26 (43.3)	25 (43.9)
Carfilzomib	18 (30.0)	16 (28.1)
Cyclophosphamide	15 (25.0)	14 (24.6)
Bortezomib	11 (18.3)	11 (19.3)
Lenalidomide	11 (18.3)	8 (14.0)
Pomalidomide	9 (15.0)	10 (17.5)
Bendamustine	7 (11.7)	7 (12.3)
Isatuximab	6 (10.0)	3 (5.3)
Prednisone	5 (8.3)	1 (1.8)
Melphalan	4 (6.7)	4 (7.0)
Doxorubicin	3 (5.0)	3 (5.3)
Etoposid	3 (5.0)	3 (5.3)
Investigational antineoplastic drugs	3 (5.0)	6 (10.5)
Ixazomib	3 (5.0)	1 (1.8)
Prednisolone	2 (3.3)	1 (1.8)
Thalidomide	2 (3.3)	2 (3.5)
Antilymphocyte immunoglobulins	1 (1.7)	0 (0.0)
Carmustine	1 (1.7)	0 (0.0)
Cisplatin	1 (1.7)	1 (1.8)
Corticosteroids	1 (1.7)	0 (0.0)
Donor lymphocyte infusion	1 (1.7)	1 (1.8)
Elotuzumab	1 (1.7)	5 (8.8)
Fludarabine	1 (1.7)	1 (1.8)
Immunological investigational substance	1 (1.7)	2 (3.5)
Panobinostat	1 (1.7)	2 (3.5)
Selinexor	1 (1.7)	2 (3.5)
Salvage stem cell transplantation	1 (1.7)	2 (3.5)
Treosulfan	1 (1.7)	0 (0.0)
Tretinoin	1 (1.7)	0 (0.0)
Vincristine	1 (1.7)	0 (0.0)
Clarithromycin	0 (0.0)	1 (1.8)
Gemcitabine	0 (0.0)	1 (1.8)
Nivolumab	0 (0.0)	1 (1.8)

Table 11: Subsequent systemic therapies – RCT, direct comparison: elotuzumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone (multipage table)

Study Drug	Patients with subsequent therapy n (%)[a]	
	Elotuzumab + pomalidomide + dexamethasone N = 60	Pomalidomide + dexamethasone N = 57
Venetoclax	0 (0.0)	1 (1.8)

a. Patients may have been treated with more than 1 drug.

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

Overall, the proportion of patients with subsequent treatment of multiple myeloma was similar in the intervention and comparator arms at the present 3rd data cut-off (70.0% versus 68.4%). This is plausible considering that, by the 3rd data cut-off, about 95% of patients in both study arms had discontinued treatment (see Table 9). For most therapies, the 2 arms exhibit similar percentages.

Nearly all included patients had received both lenalidomide and a proteasome inhibitor (e.g. carfilzomib or bortezomib) as prior therapy. These drugs were also used again to a relevant extent as subsequent treatments. According to the guideline for the diagnosis and therapy of haematological and oncological diseases [20], drugs with good tolerance and response can be used again in late lines of therapy after previous treatment attempts. At the 2nd data cut-off, the proportion of patients who showed an initial response to prior therapy with lenalidomide and/or a proteasome inhibitor before suffering a relapse corresponds approximately to the distribution of subsequent therapies. The data which have meanwhile become available, in contrast, show that the proportion of patients treated with lenalidomide and/or proteasome inhibitor in subsequent therapy is larger than the proportion of patients who had not yet been refractory to this therapy at enrolment. For instance, 18.3% of patients in the intervention arm received lenalidomide in subsequent therapy, despite the fact that 90.0% of the patients in this arm had been refractory to lenalidomide at enrolment.

Despite the ELOQUENT-3 study disallowing any switches from the comparator arm to the intervention arm, 9% of patients from the comparator arm received elotuzumab as subsequent therapy, compared to only 2% of patients in the intervention arm. However, the data submitted by the company do not show the combination in which elotuzumab was administered. In the present therapeutic indication, use in combination with lenalidomide and dexamethasone is also approved after at least 1 prior therapy. The proportions of patients who received pomalidomide as part of subsequent therapy was comparable between the arms (15.0% versus 17.5%).

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: elotuzumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone

Study	Adequate random sequence generation	Allocation concealment	Blinding		Results-independent reporting	Lack of other aspects	Risk of bias at study level
			Patients	Treatment providers			
ELOQUENT-3	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes is rated as low for the ELOQUENT-3 study. This concurs with the company's assessment.

Restrictions resulting from the open-label study design are described in Section 2.4 under risk of bias at outcome level.

Transferability of the study results to the German healthcare context

Using the following three arguments, the company is of the opinion that the results of the ELOQUENT-3 study can be extrapolated to the German healthcare context. First, the study was conducted in Germany and other European Union member states as well as the United States and Canada. Second, the dosing of the study medication is in accordance with approval in Germany. Third, the described prior and subsequent therapies cover the range of drugs available in Germany. About a fifth of the study population comes from Asia. The company argues that no relevant differences exist in comparison with Western patients with regard to disease symptoms, cytogenetic profile, and clinical parameters for which an influence on survival has been described.

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

2.4 Results on added benefit

2.4.1 Outcomes included

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

- Mortality
  - Overall survival
- Morbidity
  - Health status as recorded using the visual analogue scale of the EQ-5D VAS

- Symptoms recorded using the M.D. Anderson Symptom Inventory Multiple Myeloma Module (MDASI-MM)
  - Symptom severity, recorded using the total score of the MDASI-MM symptom scales.
  - Symptom interference with daily life, recorded with the MDASI-MM Symptom Interference Score
- Health-related quality of life
- Side effects
  - Total rate of SAEs
  - Total rate of severe AEs (CTCAE grade ≥ 3)
  - Total rate of discontinuation due to AEs
  - Further specific AEs, if any

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

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

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

Study	Outcomes								
	Overall survival	**Health status (EQ-5D VAS)**	**Symptom severity (MDASI-MM, Total Symptom Severity)**	**Symptom interference with daily life (MDASI-MM Symptom Interference)**	**Health-related quality of life**	**SAEs**	**Severe AEs (CTCAE grade ≥ 3)**	**Discontinuation due to AEs (≥ 1 drug component)**	**Specific AEs**
ELOQUENT-3	Yes	Yes	Yes	Yes	No[a]	Yes	Yes	Yes	No[b]

a. Outcome not recorded (the company allocated the MDASI-MM subscales of Activity Interference, Affective Interference, and Symptom Interference to the outcome category of health-related quality of life, see Section 2.4.1).
b. No further specific AEs were identified.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; MDASI-MM: M.D. Anderson Symptom Inventory – Multiple Myeloma Module; RCT: randomized controlled study; SAE: serious adverse event; VAS: visual analogue scale

Comments on the included outcomes and analyses

Health status (EQ-5D VAS)

For the main analysis of EQ-5D VAS, the company presents continuous analyses (difference in mean values compared to baseline). In addition to the main analysis performed via MMRM, the company has presented responder analyses for both time to first deterioration and time to definitive deterioration by 7 points, 10 points, and 15 points.

The analyses with a threshold of 7 points and 10 points are disregarded in this benefit assessment. As discussed in the IQWiG General Methods [1,24], a response criterion should be predefined to cover at least 15% of the range of an instrument's scale (for post hoc analyses, exactly 15% of the range of the scale) in order to reflect with sufficient certainty a change that is perceivable for patients.

The EQ-5D VAS responder analyses with thresholds of 7 points and 10 points as presented by the company are provided as supplementary information in Appendix D of the full dossier assessment.

The analyses with a 15-point threshold meet the above requirements and are therefore included in the assessment.

The company defines definitive deterioration as a deterioration from baseline by at least the response threshold without subsequent improvement to a level above the response threshold. However, time to definitive deterioration was disregarded since the company had provided neither an exact description of the operationalization of definitive deterioration nor an exact description of the censoring system.

Consequently, the present benefit assessment uses responder analyses of time to first deterioration by 15 points (corresponds to 15% of the scale range).

Symptoms (MDASI-MM)

MDASI-MM is a questionnaire measuring symptom severity and symptom interference with daily life in multiple myeloma patients. As was done in the previous assessment A19-80 [17], the respective total scores of all items (Total Symptom Severity and Symptom Interference) are included in the assessment of symptom severity and symptom interference with daily life and are allocated to the outcome category of morbidity. Analogously to the procedure used for EQ-5D VAS, the analyses of time to first deterioration by ≥ 1.5 points were used (corresponding to 15% of the scale range of the individual subscales of the MDASI-MM).

Side effects

For all side effect outcomes, the company disregarded the preferred terms (PTs) malignant neoplasm progression, bone metastases, plasma cell leukaemia, and plasma cell myeloma because there is a very high probability of them representing progression of the underlying disease. This approach is appropriate.

2.4.2 Risk of bias

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

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

Study	Study level	Outcomes								
		Overall survival	Health status (EQ-5D VAS)	Symptom severity (MDASI-MM, Total Symptom Severity)	Symptom interference with daily life (MDASI-MM Symptom Interference)	Health-related quality of life	SAEs	Severe AEs (CTCAE grade ≥ 3)	Discontinuation due to AEs	Specific AEs
ELOQUENT-3	L	L	H[a, b]	H[a, b]	H[a, b]	–[c]	H[b]	H[b]	H[d]	–

a. Lack of blinding in the presence of subjective recording of outcomes.
b. Incomplete observations for potentially informative reasons; difference in follow-up durations between treatment arms.
c. Outcome not recorded (the company allocated the MDASI-MM subscales of Activity Interference, Affective Interference, and Symptom Interference to the outcome category of health-related quality of life, see Section 2.4.1).
d. Lack of blinding in the presence of subjective decision on treatment discontinuation.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; H: high; MDASI-MM: M.D. Anderson Symptom Inventory – Multiple Myeloma Module; L: low; RCT: randomized controlled study; SAE: serious adverse event; VAS: visual analogue scale

The results for all relevant outcomes except overall survival are potentially highly biased. The reasons for this bias vary by outcome:

The risk of bias regarding the results for outcomes of the health status and symptoms is high because, firstly, the questionnaires survey patients' subjective opinions. Secondly, return rates differ between study arms and decrease over the course of the study. The company's dossier does not cite any reasons for this (see Section 2.3.2). Due to the open-label study design, the company likewise rated the risk of bias for the results of these outcomes as high.

For the outcomes of SAEs and severe AEs (CTCAE grade ≥ 3), the risk of bias of results is deemed high due to potentially informative censoring. For this reason, the company likewise rates the risk of bias for the results of these outcomes as high.

Concurring with the company, the lack of blinding in the presence of a subjective decision on treatment discontinuation is deemed to lead to high risk of bias for the outcome of discontinuation due to AEs (≥ 1 drug component).

2.4.3 Results

Table 15 summarizes the results on the comparison of elotuzumab + pomalidomide + dexamethasone with pomalidomide + dexamethasone in patients with relapsed and refractory multiple myeloma who have received at least 2 prior therapies including lenalidomide and/or a proteasome inhibitor. Where necessary, calculations conducted by IQWiG are provided in addition to the data from the company's dossier. The Kaplan-Meier curves for the outcomes of overall survival, severe AEs, SAEs, and treatment discontinuation due to AEs are presented in Appendix B of the full dossier assessment. No Kaplan-Meier curves are available on the morbidity outcomes.

Table 15: Results (mortality, morbidity, side effects) – RCT, direct comparison: elotuzumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone (multipage table)

Study **Outcome category** **Outcome**	**Elotuzumab + pomalidomide + dexamethasone**		**Pomalidomide + dexamethasone**		**Elotuzumab + 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]; p-value[a]**
ELOQUENT-3					
Mortality					
Overall survival	60	29.80 [22.87; 45.67] 37 (61.7)	57	17.41 [13.83; 27.70] 41 (71.9)	0.59 [0.37; 0.93]; 0.022[b]
Morbidity					
Health status					
EQ-5D VAS[c]	60	6.51 [2.79; NC] 29 (48.3)	57	3.75 [1.91; NC] 25 (43.9)	0.95 [0.53; 1.70]; 0.871
Symptom severity					
MDASI-MM Total Symptom Severity[d]	60	24.90 [6.31; NC] 23 (38.3)	57	16.43 [7.43; 34.37] 16 (28.1)	0.995 [0.50; 1.99]; 0.989
Symptom interference with daily life					
MDASI-MM Symptom Interference[d]	60	4.70 [2.83; 11.10] 32 (53.3)	57	4.67 [1.91; 32.92] 22 (38.6)	1.18 [0.66; 2.11]; 0.576
Side effects[e]					
AEs (supplementary information)	60	0.23 [0.10; 0.26] 58 (96.7)	55	0.10 [0.03; 0.26] 53 (96.4)	–
SAEs	60	9.20 [3.35; 17.31] 41 (68.3)	55	7.23 [3.32; 40.25] 29 (52.7)	0.98 [0.59; 1.63]; 0.936
Severe AEs (CTCAE grade ≥ 3)	60	3.19 [0.72; 10.12] 43 (71.7)	55	0.72 [0.69; 2.00] 44 (80.0)	0.62 [0.40; 0.97]; 0.036
Discontinuation due to AEs [f, g]	60	NR [NC; NC] 11 (18.3)	55	NR [40.25; NC] 12 (21.8)	0.66 [0.29; 1.52]; 0.326

Table 15: Results (mortality, morbidity, side effects) – RCT, direct comparison: elotuzumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone (multipage table)

Study Outcome category Outcome	Elotuzumab + pomalidomide + dexamethasone		Pomalidomide + dexamethasone		Elotuzumab + 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]; p-value[a]
a. HR, CI, and p-value (unless otherwise indicated): Cox proportional hazards model, stratified by number of prior lines of therapy (2–3 vs. ≥ 4) and ISS disease stage at baseline (I–II vs. III). b. p-value: Log-rank test stratified by number of prior lines of therapy (2–3 vs. ≥ 4) and ISS disease stage at baseline (I–II vs. III). c. Time to first deterioration, defined as a score decrease by ≥ 15 points from baseline (corresponds to 15% of the scale range [scale range of 0 to 100]). d. Time to first deterioration, defined as a score increase by ≥ 1.5 points from baseline (corresponds to 15% of the scale range [scale range of 0 to 10]). e. Recorded until 60 days after the end of treatment; the following PTs, which represent progression of multiple myeloma, were disregarded in the analysis: malignant neoplasm progression, bone metastases, plasma cell leukaemia, plasma cell myeloma. f. Discontinuation of ≥ 1 drug component. g. The ELOQUENT-3 study's 3 data cut-offs exhibit unexplained minor discrepancies in the data on discontinuation due to AEs regarding the level of SOCs and PTs. These discrepancies are not deemed to result in any relevant effects. AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; ISS: International Staging System; ND: no data; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; NR: not reached; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: system organ class				

On the basis of the available information, at most indications can be derived for the outcome of overall survival; due to high risk of bias, at most hints can be derived for all other relevant outcomes.

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference in favour of elotuzumab + pomalidomide + dexamethasone was found. However, there is an effect modification by the attribute of prior stem cell transplantation (yes/no) (see Section 2.4.4). For patients without prior stem cell transplantation, this results in an indication of added benefit in comparison with the ACT. For patients with prior stem cell transplantation, no indication of added benefit of elotuzumab + pomalidomide + dexamethasone was found; hence, there is no proof of added benefit for these patients.

This departs from the assessment submitted by the company, which derived an indication of added benefit on the basis of the total population.

Morbidity

Health status (EQ-5D VAS)

For the outcome of health status, surveyed using the EQ-5D VAS, there was no statistically significant difference between treatment groups. This results in no hint of added benefit of elotuzumab + pomalidomide + dexamethasone in comparison with the ACT; an added benefit is therefore not proven.

This concurs with the company's assessment.

Symptoms

Outcomes regarding symptoms were surveyed using the M. D. Anderson Symptom Inventory – Multiple Myeloma Module (MDASI-MM).

Symptom severity (MDASI-MM, Total Symptom Severity Score)

For the outcome of symptom severity, no statistically significant difference between treatment groups was found. This results in no hint of added benefit of elotuzumab + pomalidomide + dexamethasone in comparison with the ACT; an added benefit is therefore not proven.

This concurs with the company's assessment.

Symptom interference with daily life (MDASI-MM Symptom Interference Score)

For the outcome of symptom interference with daily life, no statistically significant difference between treatment groups was found. This results in no hint of added benefit of elotuzumab + pomalidomide + dexamethasone in comparison with the ACT; an added benefit is therefore not proven.

This concurs with the company's assessment.

Health-related quality of life

The outcome of health-related quality of life was not surveyed by the ELOQUENT-3 study.

This departs from the view held by the company, which grouped interference due to symptoms of the disease, as measured using the MDASI-MM Symptom Interference Score, under the category of health-related quality of life (see Section 2.4.1).

Side effects

For all side effect outcomes, the company disregarded the PTs malignant neoplasm progression, bone metastases, plasma cell leukaemia, and plasma cell myeloma because there is a very high probability of them representing progression of the underlying disease. Conceivably, additional PTs which can represent symptoms and complications of the underlying illness may have been recorded in the available analyses of AEs. Regarding total rates of SAEs, severe AEs (CTCAE grade ≥ 3), and discontinuation due to AEs, it is unclear whether these events impact results to

a meaningful extent. See Appendix C of the full dossier assessment for an illustration of events from common AEs.

SAEs

For the outcome of SAEs, no statistically significant difference between treatment groups was found. This results in no hint of greater or lesser harm from elotuzumab + pomalidomide + dexamethasone in comparison with the ACT; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Severe AEs (CTCAE grade ≥ 3)

For the outcome of severe AEs (CTCAE grade ≥ 3), a statistically significant difference in favour of elotuzumab + pomalidomide + dexamethasone was found. However, there is an effect modification by the attribute of number of prior lines of therapy (see Section 2.4.4). For patients with 2 to 3 prior lines of therapy, this results in a hint of lesser harm from elotuzumab + pomalidomide + dexamethasone in comparison with the ACT. For patients with ≥ 4 prior lines of therapy, there is no hint of greater or lesser harm from elotuzumab + pomalidomide + dexamethasone; greater or lesser harm is therefore not proven for these patients.

This departs from the assessment by the company, which derives a hint of added benefit on the basis of the total population.

Discontinuation due to AEs

For the outcome of discontinuation due to AEs, no statistically significant difference between treatment groups was found. This results in no hint of greater or lesser harm from elotuzumab + pomalidomide + dexamethasone in comparison with the ACT; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics are relevant for the present benefit assessment:

- Age (< 75 versus ≥ 75 years)
- Sex (female versus male)
- ISS disease stage at baseline (I vs. II vs. III)
- Number of prior lines of therapy (2 to 3 versus ≥ 4)
- Prior stem cell therapy (yes versus no)

The corresponding subgroup analyses had been predefined for the outcome of overall survival and for side effect outcomes (in this case, only for the attributes of sex and number of prior

lines of therapy). However, the company presented post hoc subgroup analyses on the above-mentioned attributes for all analysed outcomes.

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

Only results showing an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup. Table 16 presents the relevant subgroup results.

Table 16: Subgroups (mortality, side effects) – RCT, direct comparison: elotuzumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone

Study Outcome Characteristic Subgroup	Elotuzumab + pomalidomide + dexamethasone		Pomalidomide + dexamethasone		Elotuzumab + 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]
ELOQUENT-3						
Overall survival						
Prior stem cell therapy						
Yes	31	26.64 [18.04; 34.14] 23 (74.2)	33	27.70 [13.83; 37.13] 21 (63.6)	1.05 [0.58; 1.90]	0.865
No	29	48.59 [15.70; NC] 14 (48.3)	24	14.62 [6.80; 16.89] 20 (83.3)	0.33 [0.16; 0.67]	0.001
Total					Interaction[c]:	0.008
Severe AEs (CTCAE grade ≥ 3)[d]						
Number of prior lines of therapy						
2–3	35	7.89 [1.54; 24.11] 22 (62.9)	35	0.72 [0.62; 1.41] 31 (88.6)	0.38 [0.22; 0.69]	0.001
≥ 4	25	0.79 [0.49; 6.47] 21 (84.0)	20	2.40 [0.49; 12.85] 13 (65.0)	1.26 [0.62; 2.54]	0.523
Total					Interaction[c]:	0.007

a. HR and CI: nonstratified Cox proportional hazards model.
b. p-value: nonstratified log rank test.
c. p-value from interaction testing in the nonstratified Cox proportional hazards model with subgroup attribute as covariate and the interaction term "treatment*subgroup attribute".
d. Recorded until 60 days after the end of treatment; the following PTs, which represent progression of multiple myeloma, were disregarded in the analysis: malignant neoplasm progression, bone metastases, plasma cell leukaemia, plasma cell myeloma.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; PT: preferred term; RCT: randomized controlled trial

Mortality

Overall survival

For the outcome of overall survival, there is an effect modification by the attribute of prior stem cell transplantation (yes/no).

For patients without prior stem cell therapy, there is a statistically significant effect in favour of elotuzumab + pomalidomide + dexamethasone. This results in an indication of added benefit in comparison with the ACT.

No statistically significant difference between treatment groups was found for patients with prior stem cell therapy. This results in no indication of added benefit of elotuzumab + pomalidomide + dexamethasone in comparison with the ACT; an added benefit is therefore not proven.

This departs from the company's approach, which did not assess added benefit for the separate subgroups.

Side effects

Severe AEs (CTCAE grade ≥ 3)

For the outcome of severe AEs (CTCAE grade ≥ 3), there is an effect modification by the attribute of prior lines of therapy.

For patients with 2 or 3 prior lines of therapy, there is a statistically significant effect in favour of elotuzumab + pomalidomide + dexamethasone. This results in a hint of lesser harm in comparison with the ACT.

No statistically significant difference between treatment groups was found for patients with 4 or more prior lines of therapy. This results in no hint of greater or lesser harm from elotuzumab + pomalidomide + dexamethasone in comparison with the ACT; greater or lesser harm is therefore not proven.

2.5 Probability and extent of added benefit

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

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

2.5.1 Assessment of added benefit at outcome level

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

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

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Elotuzumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
Overall survival Prior stem cell therapy Yes	26.64 vs. 27.70 months HR: 1.05 [0.58; 1.90]; p = 0.865	Lesser/added benefit not proven
No	48.59 vs. 14.62 months HR: 0.33 [0.16; 0.67]; p = 0.001 Probability: Indication	Outcome category: Mortality $CI_u < 0.85$ Added benefit; extent: major
Morbidity		
Health status (EQ-5D VAS)	6.51 vs. 3.75 months HR: 0.95 [0.53; 1.70]; p = 0.871	Lesser/added benefit not proven
Symptom severity (MDASI-MM Total Symptom Severity)	24.90 vs. 16.43 months HR: 0.995 [0.50; 1.99]; p = 0.989	Lesser/added benefit not proven
Symptom interference with daily life (MDASI-MM Symptom Interference)	4.70 vs. 4.67 months HR: 1.18 [0.66; 2.11]; p = 0.576	Lesser/added benefit not proven
Health-related quality of life		
No data available[c]		
Side effects		
SAEs	9.20 vs. 7.23 months HR: 0.98 [0.59; 1.63]; p = 0.936	Greater/lesser harm not proven

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

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Elotuzumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Severe AEs (CTCAE grade ≥ 3)		
Number of prior lines of therapy		
2–3	7.89 vs. 0.72 months HR: 0.38 [0.22; 0.69]; p = 0.001 Probability: hint	Outcome category: serious/severe AEs CI_u < 0.75 and risk ≥ 5% Lesser harm; extent: major
≥ 4	0.79 vs. 2.40 months HR: 1.26 [0.62; 2.54]; p = 0.523	Greater/lesser harm not proven
Discontinuation due to AEs (≥ 1 drug component)	NR vs. NR HR: 0.66 [0.29; 1.52]; p = 0.326	Greater/lesser harm not proven

a. Probability is stated whenever a statistically significant and relevant effect is present.
b. Estimations of effect size are made depending on the outcome category, with different limits according to the upper limit of the confidence interval (CI_u).
c. The company allocated the MDASI-MM subscales of Activity Interference, Affective Interference, and Symptom Interference to the outcome category of health-related quality of life (see Section 2.4.1).

AE: adverse event; CI: confidence interval; CI_u: upper limit of CI; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life – 5 Dimensions; HR: hazard ratio; MDASI-MM: M.D. Anderson Symptom Inventory – Multiple Myeloma; NR: not reached; SAE: serious adverse event; VAS: visual analogue scale

2.5.2 Overall conclusion on added benefit

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

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

Favourable effects	**Unfavourable effects**
Mortality ▪ Overall survival ▫ Prior stem cell therapy (no): Indication of added benefit – extent: major	–
Serious/severe side effects ▪ Severe AEs (CTCAE grade ≥ 3): ▫ Number of prior lines of therapy (2–3): Hint of lesser harm – extent: considerable	
The company's dossier does not provide any data on health-related quality of life. The company allocated the MDASI-MM subscales of Activity Interference, Affective Interference, and Symptom Interference to the outcome category of health-related quality of life (see Section 2.4.1).	
AEs: adverse events; CTCAE: Common Terminology Criteria for Adverse Events; MDASI-MM: M. D. Anderson Symptom Inventory – Multiple Myeloma Module	

Overall, exclusively favourable effects of various certainties of results (indication or hint) were found for elotuzumab + pomalidomide + dexamethasone versus pomalidomide + dexamethasone for the outcome categories of mortality and side effects, each of them applying only to subpopulations.

Regarding the outcome of overall survival, an indication of major added benefit was found for patients without prior stem cell therapy. There is a hint of lesser harm for the outcome of severe AEs (CTCAE grade ≥ 3) for patients with 2 to 3 prior lines of therapy.

Taking into account both effect modifications for the 2 outcomes, no meaningful summary interpretation of results can be derived from the available information. Due to the fatal course of disease, the outcome of overall survival is attributed greater relevance in this situation; therefore, this outcome is considered a priority. As a consequence, due to the effect modification for the outcome of overall survival, only the attribute of prior stem cell transplantation (yes/no) is used for the overall conclusion on added benefit.

In summary, there is an indication of major added benefit of elotuzumab + pomalidomide + dexamethasone in comparison with the ACT for adult patients with relapsed and refractory multiple myeloma who have received at least 2 prior therapies including lenalidomide and a proteasome inhibitor, have demonstrated disease progression on the most recent therapy, and received no prior stem cell therapy. No added benefit has been proven for patients who received prior stem cell therapy.

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

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

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Treatment of adult patients with relapsed and refractory multiple myeloma who have received at least 2 prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on 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 ▪ 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	Patients **without** prior stem cell therapy: ▪ Indication of major added benefit
		Patients **with** prior stem cell therapy: ▪ Added benefit not proven
a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is marked in **bold**. b. High-dose chemotherapy with stem cell transplantation is assumed not to be an option for patients at the time of the current therapy. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The assessment described above departs from that made by the company, which has derived an indication of considerable added benefit for all patients, irrespective of any prior stem cell therapy.

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

Supplementary note on the ACT

After dossier submission, the G-BA modified the ACT by including bortezomib in combination with pegylated liposomal doxorubicin as an additional option for the ACT. The present benefit assessment is based on the originally specified ACT. Implementation of the modified ACT would not affect the relevance of the data used in this benefit assessment.

References for English extract

Please see full dossier assessment for full reference list.

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

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