IQWiG Reports – Commission No. A19-80

Elotuzumab (multiple myeloma) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Elotuzumab (multiples Myelom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 20 December 2019). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ISS	International Staging System
MDASI-MM	MD Anderson Symptom Inventory for multiple myeloma
PFS	progression-free survival
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug elotuzumab. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 20 September 2019.

Research question

The aim of the present report is the assessment of the added benefit of elotuzumab in combination with pomalidomide and dexamethasone compared with the appropriate comparator therapy (ACT) in the 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.

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

Table 2: Research questions of the benefit assessment of elotuzumab

Research question	Therapeutic indication	ACT[a]
1	Elotuzumab in combination with pomalidomide and dexamethasone for the treatment of relapsed and refractory multiple myeloma in adult patients 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. 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 on the ACT. The company chose pomalidomide in combination with dexamethasone from the options mentioned.

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

Results

Study pool and study characteristics

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

The ELOQUENT-3 study is an ongoing RCT comparing a triple combination of elotuzumab, pomalidomide and dexamethasone with the dual combination of pomalidomide and dexamethasone. The study is conducted in adult patients with relapsed and refractory multiple myeloma who received at least 2 prior therapies. They 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 last prior therapy.

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.

The study includes a total of 117 randomized patients. Neither patients nor study staff are blinded to the treatment. Stratification was made according to the number of prior lines of treatment (2–3 versus ≥ 4) and International Staging System (ISS) stage at baseline (I–II versus III). Switching from the comparator therapy (pomalidomide + dexamethasone) to the intervention therapy (triple combination of elotuzumab + pomalidomide + dexamethasone) is not possible.

Dosage and administration schemes of the study medications used in the study correspond to the recommendations provided in the respective Summaries of Product Characteristics (SPCs).

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. A first predefined data cut-off from 21 February 2018 was conducted after reaching a specified number of progression events. The second data cut-off was requested by the European Medicines Agency (EMA) in the framework of the approval process to obtain current data on overall survival, and was conducted on 29 November 2018. The second data cut-off was the basis for the present benefit assessment.

Risk of bias at study and outcome level

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 health status and symptoms 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 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 AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)" was rated as high. Concurring with the company, the lack of blinding in subjective decision-making to discontinue treatment was seen as a reason for a high risk of bias for the outcome "discontinuation due to AEs" (≥ 1 drug component).

Overall, 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 all other relevant outcomes.

Results

Mortality – overall survival

A statistically significant difference in favour of elotuzumab + pomalidomide + dexamethasone was shown for the outcome "overall survival". This resulted in an indication of an added benefit in comparison with the ACT.

Morbidity – health status

No statistically significant difference between the treatment groups was shown for the outcome "health status" recorded using the European Quality of Life-5 Dimensions visual analogue scale (EQ-5D VAS). This resulted in no hint of an added benefit of elotuzumab + pomalidomide + dexamethasone in comparison with the ACT; an added benefit is therefore not proven.

Morbidity – symptoms

Symptom outcomes were recorded using the MD Anderson Symptom Inventory for multiple myeloma (MDASI-MM).

Symptom severity

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

Impact of symptoms on daily functioning

There was no statistically significant difference between the treatment groups for the outcome "impact of symptoms on daily functioning". This resulted in no hint of an 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 "health-related quality of life" was not recorded in the ELOQUENT-3 study.

Side effects

Serious adverse events

There was no statistically significant difference between the treatment groups for the outcome "SAEs". This resulted in no hint of greater or lesser harm of elotuzumab + pomalidomide + dexamethasone in comparison with the ACT; an added benefit is therefore not proven.

Severe adverse events (CTCAE grade 3–4)

There was an effect modification by the characteristic of number of prior lines of treatment for the outcome "severe AEs (CTCAE grade 3–4)".

A statistically significant effect in favour of elotuzumab + pomalidomide + dexamethasone was shown for patients with 2 or 3 prior lines of treatment. This resulted in a hint of lesser harm in comparison with the ACT.

There was no statistically significant difference between the treatment groups for patients with 4 or more prior lines of treatment. This resulted in no hint of greater or lesser harm of elotuzumab + pomalidomide + dexamethasone in comparison with the ACT; an added benefit is therefore not proven.

Discontinuations due to adverse events

There was no statistically significant difference between the treatment groups for the outcome "discontinuations due to AEs". This resulted in no hint of greater or lesser harm of elotuzumab + pomalidomide + dexamethasone in comparison with the ACT; an added benefit is therefore not proven.

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

Based on the results presented, probability and extent of the added benefit of the drug elotuzumab in comparison with the ACT are assessed as follows:

[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].

Overall, only positive effects with different certainty of results (indication or hint) were found for elotuzumab + pomalidomide + dexamethasone versus pomalidomide + dexamethasone in the outcome categories of mortality and side effects. The positive effect in side effects was only shown in patients who had received 2 or 3 lines of treatment before enrolment.

In summary, there is an indication of a minor added benefit of elotuzumab + pomalidomide + dexamethasone versus pomalidomide + dexamethasone for 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.

Table 3 shows a summary of probability and extent of the added benefit of elotuzumab.

Table 3: Elotuzumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Elotuzumab in combination with pomalidomide and dexamethasone for the treatment of relapsed and refractory multiple myeloma in adult patients 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	Indication of minor added benefit

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 deriving 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 elotuzumab in combination with pomalidomide and dexamethasone compared with the ACT in the 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.

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

Table 4: Research questions of the benefit assessment of elotuzumab

Research question	Therapeutic indication	ACT[a]
1	Elotuzumab in combination with pomalidomide and dexamethasone for the treatment of relapsed and refractory multiple myeloma in adult patients 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. 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 on the ACT. The company chose pomalidomide in combination with dexamethasone from the options mentioned.

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

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 elotuzumab (status: 23 July 2019)
- bibliographical literature search on elotuzumab (last search on 23 July 2019)
- search in trial registries for studies on elotuzumab (last search on 23 July 2019)

To check the completeness of the study pool:

- search in trial registries for studies on elotuzumab (last search on 25 September 2019)

The check identified no additional relevant study.

2.3.1 Studies included

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

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

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	**Sponsored study[a] (yes/no)**	**Third-party study (yes/no)**
CA204-125 (ELOQUENT-3[b])	Yes	Yes	No
a. Study for which the company was sponsor. b. In the following tables, the study is referred to with this abbreviated form. RCT: randomized controlled trial; vs.: versus			

The study pool concurs with that of the company. Section 2.6 contains a reference list for the study included.

2.3.2 Study characteristics

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

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ELOQUENT-3	RCT, open-label, parallel	Patients ≥ 18 years with relapsed and refractory[b] multiple myeloma ▪ with ≥ 2 prior therapies, including ≥ 2 consecutive cycles with lenalidomide and/or a proteasome inhibitor ▪ ECOG PS ≤ 2	Elotuzumab + pomalidomide + dexamethasone (N = 60) pomalidomide + dexamethasone (N = 57)	Screening: 28 days maximum Treatment: in 28-day cycles until disease progression, occurrence of unacceptable toxicity, withdrawal of consent, termination of study by the sponsor, initiation of another antimyeloma therapy Observation[c]: outcome-specific, at most until death, discontinuation of study participation or termination of study by the sponsor	39 centres in Canada, France, Germany, Greece, Italy, Japan, Netherlands, Poland, Spain, USA 3/2016–ongoing (follow-up for overall survival ongoing) First data cut-off: 21 Feb 2018 Second data cut-off: 29 Nov 2018	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 exclusively contain information on the relevant available outcomes for this benefit assessment.
b. Refractory to last pretreatment (irrespective of drug) and relapsed or refractory to prior therapy with lenalidomide or proteasome inhibitor. See Section 2.2 for a definition of refractoriness and relapse.
c. Outcome-specific information is provided in Table 8.

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

Table 7: Characteristics 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 IV, on days 1, 8, 15 and 22 of each cycle ▪ from cycle 3: 20 mg/kg IV, on day 1 of each cycle Pomalidomide: ▪ 4 mg orally once daily, on days 1–21 of each cycle ▪ dose interruption in case of thrombocytopenia and neutropenia; treatment continuation with 3 mg after normalization, reduction by another 1 mg in case of further deterioration Dexamethasone[c]: ▪ cycles 1 + 2: on days 1, 8, 15, 22 ▫ ≤ 75 years: 28 mg orally + 8 mg IV ▫ > 75 years: 8 mg orally + 8 mg IV[b] ▪ from cycle 3: on days 1, 8, 15, 22 ▫ ≤ 75 years: day 1: 28 mg orally + 8 mg IV; days 8, 15, 22: 40 mg orally ▫ > 75 years: day 1: 8 mg orally + 8 mg IV[b]; days 8, 15, 22: 20 mg orally ▪ dose reduction/interruption depending on observed side effect[b]	Pomalidomide: ▪ 4 mg orally once daily, on days 1–21 of each cycle[a] ▪ dose interruption in case of thrombocytopenia and neutropenia; treatment continuation with 3 mg after normalization, reduction by another 1 mg in case of further deterioration Dexamethasone: ▪ ≥ 75 years: 40 mg orally on days 1, 8, 15, 22 of each cycle ▪ > 75 years: 20 mg orally on days 1, 8, 15, 22 of each cycle ▪ dose reduction depending on observed side effect
	Discontinuation of one component of the study medication does not necessarily lead to discontinuation of all drugs; it is also possible to continue treatment with individual components or a dual combination	
	Premedication before elotuzumab: ▪ H1 and H2 blockers (e.g. diphenhydramine or ranitidine), paracetamol **Non-permitted pretreatment:** ▪ autologous stem cell transplantation within 12 weeks before start of treatment ▪ allogeneic stem cell transplantation within 12 months before start of treatment ▪ pomalidomide ▪ melphalan or monoclonal antibodies **Concomitant treatment** <u>mandatory</u>: ▪ thrombosis prophylaxis (e.g. acetylsalicylic acid, low molecular weight heparin, vitamin K antagonists) <u>as needed:</u> ▪ treatment of infusion reactions (e.g. IV corticosteroids, H2 inhibitors, leukotriene inhibitors), oxygen inhalation, epinephrine, bronchodilators, oral antiviral and antimicrobial prophylaxis, antiemetics, bisphosphonates, erythropoietin, G-CSF for neutropenia <u>not allowed:</u> ▪ other antimyeloma therapies within 14 days before start of treatment ▪ other steroids than dexamethasone, low-dose prednisone or low-absorption steroids ▪ other investigational treatments	

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

Study	Intervention	Comparison
a. Treatment in both study arms is in 28-day cycles. b. If the elotuzumab dose has been missed or delayed, dexamethasone is to be administered orally as in the comparator arm. c. If infusion reactions to the administration of elotuzumab occur, the intravenous part of dexamethasone is increased depending on the severity of the reaction and the oral dose is reduced accordingly to keep the total dose stable. In previous grade 2 infusion reaction, 10 mg dexamethasone IV and 28 mg dexamethasone orally were administered; in grade 3 or repeated grade 2 reaction, 18 mg IV and 2 oral doses of 8 mg each were administered. In patients ≥ 75 years of age, this regimen was followed with correspondingly lower dosages. d. Dose reduction of dexamethasone is only possible for the oral dose, the IV dose should generally be 8 mg. IV: intravenous; RCT: randomized controlled trial; vs.: versus		

The ELOQUENT-3 study is an ongoing RCT comparing a triple combination of elotuzumab, pomalidomide and dexamethasone with the dual combination of pomalidomide and dexamethasone. It is a phase 2 study, on which the approval of elotuzumab in the present therapeutic indication is based. The study is conducted in adult patients with relapsed and refractory multiple myeloma who received at least 2 prior therapies. They 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 last prior therapy.

The current version of the European Public Assessment Report (EPAR) of the EMA shows that the therapeutic indication stated in the approval, relapsed and refractory multiple myeloma, refers to the situation in the approval study ELOQUENT-3 [3]. Thus, in accordance with the inclusion criteria of the approval study, the term “relapsed and refractory multiple myeloma” covers the following requirements for treatment response or failure of prior therapies:

- refractoriness to the last prior therapy of multiple myeloma (irrespective of the drug or drug combination), and
- refractoriness to lenalidomide and/or proteasome inhibitors in the pretreatment, or
- if lenalidomide or proteasome inhibitors were not the last pretreatments: partial response to at least one treatment with these drugs before relapse.

Refractoriness is defined as disease progression on or within 60 days of treatment both in the approval study and in the guidelines. Relapse is defined as disease progression after response to treatment within 6 months [4,5].

Patients with prior treatment with pomalidomide were not allowed to participate in the ELOQUENT-3 study. This rules out an unsuitability of pomalidomide for the participating patients due to refractoriness. No other reasons are apparent that would prevent the suitability of pomalidomide. Autologous stem cell transplantation within 12 weeks before the start of the study and allogeneic stem cell transplantation within 12 months before the start of the study

were also excluded. Based on the therapeutic algorithm in the guidelines, however, it is assumed that high-dose chemotherapy with subsequent stem cell transplantation was not indicated on enrolment for patients without previous stem cell transplantation in the present therapeutic indication [4,5].

The study includes a total of 117 randomized patients. Neither patients nor study staff are blinded to the treatment. Stratification was made according to the number of prior lines of treatment (2–3 versus ≥ 4) and ISS stage at baseline (I–II versus III). Switching from the comparator therapy (pomalidomide + dexamethasone) to the intervention therapy (triple combination of elotuzumab + pomalidomide + dexamethasone) is not possible.

Dosage and administration schemes of the study medications used in the study correspond to the recommendations provided in the respective SPCs [6,7].

The primary outcome is PFS. Overall survival, symptoms, health status and AEs are recorded as patient-relevant secondary outcomes.

Two data cut-offs are available for the study. A first predefined data cut-off from 21 February 2018 was conducted after reaching a specified number of progression events. A clinical study report is available for this data cut-off. The second data cut-off was requested by the EMA in the framework of the approval process to obtain current data on overall survival, and was conducted on 29 November 2018. The results of this data cut-off are exclusively reported in Module 4 B of the dossier. A further predefined data cut-off is planned for the time point when at least 78 deaths have occurred. This data cut-off is still pending at the time of the present benefit assessment and is expected to provide the final analysis of overall survival according to the planning of the study. The present benefit assessment is based on the second data cut-off from 29 November 2018. Results on all relevant outcomes were available for this data cut-off.

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: elotuzumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone

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

a. The outcomes may have been recorded only until treatment discontinuation (see Section 2.7.4.2 of the full dossier assessment).

EQ-5D: European Quality of Life-5 Dimensions; MDASI-MM: MD Anderson Symptom Inventory for multiple myeloma; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus

The observation periods for the outcomes on side effects were systematically shortened because they were only recorded for the time period of treatment with the study medication (plus 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.

It cannot be ruled out that, contrary to the information provided in the study documents, the outcomes on health status and symptoms were only recorded until treatment discontinuation. See Section 2.7.4.2 of the full dossier assessment for more details.

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

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

Study Characteristics Category	**Elotuzumab + pomalidomide + dexamethasone**	**Pomalidomide + dexamethasone**
ELOQUENT-3	N[a] = 60	N[a] = 57
Age [years], mean (SD)	66 (10)	66 (10)
Sex [F/M], %	47/53	39/61
Family origin, n (%)		
Light-skinned	45 (75.0)	45 (78.9)
Dark-skinned/African American	0 (0.0)	1 (1.8)
Asian	15 (25.0)	9 (15.8)
Other	0 (0.0)	2 (3.5)
ECOG Performance Status		
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)	18 (31.6)
3	21 (35.0)	18 (31.6)
≥ 4	25 (41.7)	21 (36.8)

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

Study Characteristics Category	Elotuzumab + pomalidomide + dexamethasone	Pomalidomide + dexamethasone
Refractory[b], n (%)		
to lenalidomide	54 (90.0)	48 (84.2)
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[b], n (%)		
after lenalidomide	5 (8.3)	7 (12.3)
after proteasome inhibitors	13 (21.7)	8 (14.0)
after bortezomib	17 (28.3)	10 (17.5)[c]
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)[d]
Refractory to lenalidomide and relapsed after proteasome inhibitor or vice versa	18 (30.0)	9 (15.8)[e]
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 (%)	44 (73.3[f])	51 (89.5)
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. In accordance with the inclusion criteria, all patients included were refractory to their last prior therapy. See Section 2.2 for definitions of refractoriness and relapse.
c. Discrepancy between Module 4 B and Module 5 of the dossier. The information provided in the table is from Module 5. Module 4 B: 17 (28.3) vs. 9 (15.8).
d. Discrepancy between Module 4 B and Module 5 of the dossier. The information provided in the table is from Module 5. Module 4 B: 0 (0.0) vs. 4 (7.0).
e. Discrepancy between Module 4 B and Module 5 of the dossier. The information provided in the table is from Module 5. Module 4 B: 19 (31.7) vs. 8 (14.0).
f. Institute's calculation.

ECOG: Eastern Cooperative Oncology Group; F: female; M: male; n: number of patients in the category; N: number of randomized (or included) patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The patient population of the ELOQUENT-3 study shows slight differences between the treatment groups for some patient characteristics, e.g. sex, ISS stage at baseline, cytogenetic risk group, number of prior lines of treatment and prior stem cell therapies. This is probably

due to the small study population; it is assumed 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 light-skinned or of European origin, the others were mainly from the Asian region, with a higher proportion in the intervention arm. The patients' general condition was mostly good (about 90% with Eastern Cooperative Oncology Group Performance Status [ECOG PS] ≤ 1). Disease severity according to ISS stage was low in about half of the patients (stage I). Just under 52% and 58% of the patients had been treated with stem cell transplantation before enrolment. All patients had received at least 2 prior drug therapies before start of the study. Most patients were refractory to lenalidomide and/or at least one proteasome inhibitor.

Subsequent treatment of multiple myeloma in the ELOQUENT-3 study

Table 10 shows the subsequent systemic therapies received by the patients after discontinuation of the study medication.

Table 10: Subsequent systemic therapies – RCT, direct comparison: elotuzumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone

Study Drug	Elotuzumab + pomalidomide + dexamethasone	Pomalidomide + dexamethasone
ELOQUENT-3	**N = 60**	**N = 57**
Patients with subsequent therapies[a]	33 (55.0)	35 (61.4)
Dexamethasone	27 (45.0)	32 (56.1)
Daratumumab	18 (30.0)	21 (36.8)
Cyclophosphamide	10 (16.7)	10 (17.5)
Carfilzomib	8 (13.3)	13 (22.8)
Pomalidomide	8 (13.3)	8 (14.0)
Bendamustine	6 (10.0)	6 (10.5)
Bortezomib	6 (10.0)	8 (14.0)
Investigational antineoplastic drugs	4 (6.7)	4 (7.0)
Lenalidomide	4 (6.7)	7 (12.3)
Prednisone	3 (5.0)	0 (0.0)
Doxorubicin	2 (3.3)	3 (5.3)
Antilymphocyte immunoglobulins	1 (1.7)	0 (0.0)
Carmustine	1 (1.7)	0 (0.0)
Etoposide	1 (1.7)	3 (5.3)
Fludarabine	1 (1.7)	0 (0.0)
Melphalan	1 (1.7)	3 (5.3)
Panobinostat	1 (1.7)	1 (1.8)
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)
Cisplatin	0 (0.0)	1 (1.8)
Clarithromycin	0 (0.0)	1 (1.8)
Donor lymphocyte infusion	0 (0.0)	1 (1.8)
Elotuzumab	0 (0.0)	3 (5.3)
Nivolumab	0 (0.0)	1 (1.8)
Prednisolone	0 (0.0)	1 (1.8)
Thalidomide	0 (0.0)	1 (1.8)
Venetoclax	0 (0.0)	1 (1.8)

a. Patients may have been treated with more than one drug.
RCT: randomized controlled trial; vs.: versus

Overall, the proportion of patients with subsequent treatment of multiple myeloma was lower in the intervention arm than in the comparator arm (55.0% versus 61.4%). This is plausible considering the respective treatment discontinuation rates. There are also differences between the study arms for individual drugs (e.g. dexamethasone, carfilzomib and lenalidomide), with

the vast majority, in line with the overall rate, being used less frequently as a subsequent treatment in the intervention arm than in the comparator arm.

Nearly all patients included in the study 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 [4], drugs with good tolerance and response can be used again in late lines of treatment after previous treatment attempts. 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.

Observation periods and treatment durations in the ELOQUENT-3 study

Table 11 shows the median treatment duration of the patients and the median observation period for individual outcomes.

Table 11: 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	N = 60	N = 57
Treatment duration [months]		
Median [Q1; Q3]	Elotuzumab: 7.41 [2.79; 10.61] Pomalidomide: 8.05 [3.45; 10.94] Dexamethasone: 7.95 [3.48; 11.07]	Pomalidomide: 4.37 [2.53; 8.97] Dexamethasone: 4.17 [2.10; 9.00]
Observation period		
Overall survival[a]	ND	ND
Morbidity[a]	ND	ND
Health-related quality of life	No data available	
Side effects[b]	ND	ND

a. According to the study documents, observation for the outcomes on mortality and morbidity was to be up to death; see Table 8.
b. According to the study protocol, side effects were recorded until 60 days after the end of treatment.

N: number of randomized patients; ND: no data; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; vs.: versus

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. The company did not provide any information on the observation periods of the individual outcomes. For AEs, the observation period 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 observation period for AEs in the comparison arm is only about 64% of the observation period in the intervention arm (see 2.7.4.2 of the full dossier assessment). All other patient-relevant outcomes are to be observed until death; their observation period is therefore unknown.

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		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
ELOQUENT-3	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

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

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

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.4.3.2 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - health status, recorded with the VAS of the EQ-5D questionnaire
  - symptoms measured with the MDASI-MM
    - symptom severity, recorded with the total score of the MDASI-MM symptom scales

- impact of symptoms on daily functioning, recorded with the symptom interference score of the MDASI-MM

- Health-related quality of life
- Side effects
  - overall rate of SAEs
  - overall rate of severe AEs (CTCAE grade 3–4)
  - overall rate of discontinuations due to AEs
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4 B) (see Section 2.7.4.3.2 of the full dossier assessment).

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

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)**	**Impact of symptoms on daily functioning (MDASI-MM symptom interference)**	**Health-related quality of life**	**SAEs**	**Severe AEs (CTCAE grade 3–4)**	**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.
b. No usable data (see Section 2.7.4.3.2 of the full dossier assessment).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; MDASI-MM: MD Anderson Symptom Inventory for multiple myeloma; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

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: elotuzumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone

Study		Outcomes								
	Study level	Overall survival	Health status (EQ-5D VAS)	Symptom severity (MDASI-MM total symptom severity)	Impact of symptoms on daily functioning (MDASI-MM symptom interference)	Health-related quality of life	SAEs	Severe AEs (CTCAE grade 3–4)	Discontinuation due to AEs (≥ 1 drug component)	Specific AEs
ELOQUENT-3	L	L	H[a, b]	H[a, b]	H[a, b]	–[c]	H[d]	H[d]	H[e]	–[f]

a. Decreasing response rate to questionnaires in the course of the study and differential response rate between the treatment arms.
b. Lack of blinding in subjective recording of outcomes.
c. Outcome not recorded.
d. Incomplete observations for potentially informative reasons; differences in the observation periods between the treatment groups.
e. Lack of blinding in subjective decision-making to discontinue treatment.
f. No usable data (see Section 2.7.4.3.2 of the full dossier assessment).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; H: high; L: low; MDASI-MM: MD Anderson Symptom Inventory for multiple myeloma; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

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 health status and symptoms 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 decrease in the course of the study. No reasons for this were provided in the company's dossier (see Section 2.7.4.2 of the full dossier assessment). The company also rated the risk of bias as high for the results on these outcomes.

Due to potentially informative censoring, the risk of bias of the results for the outcomes "SAEs", and "severe AEs (CTCAE grade ≥ 3)" was rated as high (see Section 2.7.4.2 of the

full dossier assessment). This deviates from the assessment of the company, which regarded the risk of bias of the results on AEs as low.

Concurring with the company, the lack of blinding in subjective decision-making to discontinue treatment was seen as a reason for a high risk of bias for the outcome "discontinuation due to AEs" (≥ 1 drug component).

There were no usable data for specific AE outcomes (see Section 2.7.4.3.2 of the full dossier assessment).

2.4.3 Results

Table 15 and Table 16 summarize the results of 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 the Institute are provided in addition to the data from the company's dossier. The Kaplan-Meier curve for the outcome "overall survival" is presented in Appendix A of the full dossier assessment. No Kaplan-Meier curves are available for the AE outcomes.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: elotuzumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone

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**
ELOQUENT-3					
Mortality					
Overall survival	60	NA [29.94; NA] 20 (33.3)	57	17.41 [13.83; NA] 28 (49.1)	0.54 [0.30; 0.96]; 0.034
Side effects[a]					
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] 37 (61.7)	55	7.23 [3.32; NA] 28 (50.9)	0.99 [0.59; 1.65]; 0.958
Severe AEs (CTCAE grade 3–4)	60	5.22 [0.76; 10.15] 39 (65.0)	55	0.72 [0.69; 1.87] 43 (78.2)	0.62 [0.40; 0.98]; 0.040
Discontinuation due to AEs (≥ 1 drug component)	60	NA [NA; NA] 11 (18.3)	55	NA [NA; NA] 12 (21.8)	0.63 [0.27; 1.44]; 0.270

a. Recorded until 60 days after the end of treatment; the following PTs, which represent progression of multiple myeloma, were not considered 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 event; N: number of analysed patients; NA: not achieved; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

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

Study Outcome category Outcome	Elotuzumab + pomalidomide + dexamethasone			Pomalidomide + dexamethasone			Elotuzumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone
	N[a]	Values at baseline mean (SD)	Change end of observation mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change end of observation mean[b] (SE)	MD [95% CI]; p-value
ELOQUENT-3							
Morbidity							
Health status							
EQ-5D VAS[c]	54	65.5 (18.6)	−0.1 (2.6)	49	69.2 (20.9)	−2.2 (2.7)	2.1 [−3.2; 7.3]; 0.440
Symptom severity							
MDASI-MM total symptom severity[d]	49	1.5 (1.4)	0.6 (0.2)	41	1.6 (1.4)	0.4 (0.2)	0.2 [−0.2; 0.6]; 0.233
Impact of symptoms on daily functioning							
MDASI-MM symptom interference[d]	49	2.5 (2.7)	0.9 (0.3)	41	2.1 (2.0)	0.7 (0.4)	0.2 [−0.5; 0.9]; 0.601
Health-related quality of life							
Outcome not recorded							

a. Number of patients considered in the analysis for the calculation of the effect estimation; the values at baseline may be based on other patient numbers.
b. Unless stated otherwise, MMRM analysis of the ITT population.
c. Higher values on the scale correspond to a better health status; a positive group difference indicates an advantage of elotuzumab.
d. Higher values on the scale correspond to greater symptom severity or impairment; a negative group difference indicates an advantage of elotuzumab.

CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; ITT: intention to treat; MD: mean difference; MDASI-MM: MD Anderson Symptom Inventory for multiple myeloma; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale; vs.: versus

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 all other relevant outcomes (see Section 2.4.2).

Mortality

Overall survival

A statistically significant difference in favour of elotuzumab + pomalidomide + dexamethasone was shown for the outcome “overall survival”. This resulted in an indication of an added benefit in comparison with the ACT.

This concurs with the company’s assessment.

Morbidity

Health status (EQ-5D VAS)

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

This concurs with the company's assessment.

Symptoms

Symptom severity (MDASI-MM total symptom severity score)

There was no statistically significant difference between the treatment groups for the outcome "symptom severity". This resulted in no hint of an 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.

Impact of symptoms on daily functioning (MDASI-MM symptom interference score)

There was no statistically significant difference between the treatment groups for the outcome "impact of symptoms on daily functioning". This resulted in no hint of an 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 "health-related quality of life" was not recorded in the ELOQUENT-3 study.

This contradicts the information provided by the company, which allocated the impact of symptoms of the disease, measured with the MDASI-MM symptom interference score, to the category of health-related quality of life (see Section 2.7.4.3.2 of the full dossier assessment).

Side effects

It cannot be excluded that symptoms and complications of the underlying disease were also included in the available analyses on AEs (see Appendix B of the full dossier assessment for the presentation of events related to frequent AEs). This also applies under consideration of the approach of the company, which excluded certain events that represent a progression of the underlying disease from the analysis of AEs. Regarding the overall rate of SAEs, of severe AEs (CTCAE grade 3–4) and of the discontinuations due to AEs, these events were not assumed to have a relevant influence on the results, however.

Serious adverse events

There was no statistically significant difference between the treatment groups for the outcome "SAEs". This resulted in no hint of greater or lesser harm of elotuzumab + pomalidomide + dexamethasone in comparison with the ACT; an added benefit is therefore not proven.

This concurs with the company's assessment.

Severe adverse events (CTCAE grade 3–4)

A statistically significant difference in favour of elotuzumab + pomalidomide + dexamethasone was shown for the outcome "severe AEs (CTCAE grade 3–4)". However, there was an effect modification by the characteristic of number of prior lines of treatment. There was a hint of less harm from elotuzumab + pomalidomide + dexamethasone in comparison with the ACT for patients with 2 to 3 prior lines of treatment. For patients with ≥ 4 prior lines of treatment, there was no hint of an added benefit of elotuzumab + pomalidomide + dexamethasone; an added benefit is therefore not proven for these patients.

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

Discontinuation due to adverse events

There was no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs". This resulted in no hint of greater or lesser harm of elotuzumab + pomalidomide + dexamethasone in comparison with the ACT; an added benefit is therefore not proven.

This concurs with the company's assessment.

Specific adverse events

Overall, suitable analyses for the assessment of specific AEs were missing in the company's dossier. Due to the different observation periods between the study arms, a complete assessment of side effects can only be made on the basis of suitable event time analyses on individual AEs. The company did not present such analyses, however. On the basis of the available information on the proportions of events and the severity grades, it is not assumed that an added benefit for the outcome "overall survival" is called into question by a possible harm (see Appendix B of the full dossier assessment).

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics were considered in the present assessment:

- age (< 75 years versus ≥ 75 years)
- sex (female versus male)
- region (North America versus Europe versus Japan versus Australia)

- disease stage at baseline according to ISS (I–II versus III)
- number of prior treatment regimens (2–3 versus 4)
- prior stem cell therapy (yes versus no)

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

Only 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. Table 17 presents the relevant results for subgroups.

Table 17: Subgroups (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]**	**p-value**
ELOQUENT-3						
Severe AEs (CTCAE grade 3–4)[a]						
Number of prior lines of treatment						
2–3	35	7.89 [1.54; NA] 20 (57.1)	35	0.72 [0.62; 1.41] 31 (88.6)	0.39 [0.22; 0.69]	0.001
≥ 4	25	1.22 [0.53; 10.12] 19 (76.0)	20	2.40 [0.49; NA] 12 (60.0)	1.33 [0.65; 2.75]	0.433
Total					Interaction:	0.008

a. Recorded until 60 days after the end of treatment; the following PTs, which represent progression of multiple myeloma, were not considered 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 event; N: number of analysed patients; NA: not achieved; PT: Preferred Term; RCT: randomized controlled trial; vs.: versus

Side effects

Severe adverse events (CTCAE grade 3–4)

There was an effect modification by the characteristic of number of prior lines of treatment for the outcome “severe AEs” (CTCAE grade 3–4)

A statistically significant effect in favour of elotuzumab + pomalidomide + dexamethasone was shown for patients with 2 or 3 prior lines of treatment. This resulted in a hint of lesser harm in comparison with the ACT.

There was no statistically significant difference between the treatment groups for patients with 4 or more prior lines of treatment. This resulted in no hint of greater or lesser harm of elotuzumab + pomalidomide + dexamethasone in comparison with the ACT; an added benefit is therefore not proven.

This deviates from the approach of the company, which did not conduct an assessment of the added benefit separated by subgroups.

2.5 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below. The various outcome categories and the effect sizes were taken into account. 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 18).

Table 18: 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** **Quantile of time to event (months) or MD** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
Overall survival	NA vs. 17.41 HR: 0.54 [0.30; 0.96]; p = 0.034 probability: "indication"	Outcome category: mortality $0.95 \leq CI_u < 1.00$ added benefit, extent: "minor"
Morbidity		
Health status (EQ-5D VAS)	−0.1 vs. −2.2 MD: 2.1 [−3.2; 7.3]; p = 0.440	Lesser benefit/added benefit not proven
Symptom severity (MDASI-MM total symptom severity)	0.6 vs. 0.4 MD: 0.2 [−0.2; 0.6]; p = 0.233	Lesser benefit/added benefit not proven
Impact of symptoms on daily functioning (MDASI-MM symptom interference)	0.9 vs. 0.7 MD: 0.2 [−0.5; 0.9]; p = 0.601	Lesser benefit/added benefit not proven
Health-related quality of life		
No data available		
Side effects		
SAEs	9.20 vs. 7.23 HR: 0.99 [0.59; 1.65]; p = 0.958	Greater/lesser harm not proven
Severe AEs (CTCAE grade 3–4) Number of prior lines of treatment		
2−3	7.89 vs. 0.72 HR: 0.39 [0.22; 0.69]; p = 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk ≥ 5% lesser harm, extent: "major"
≥ 4	1.22 vs. 2.40 HR: 1.33 [0.65; 2.75]; 0.433	Greater/lesser harm not proven
Discontinuation due to AEs (≥ 1 drug component)	NA HR: 0.63 [0.27; 1.44]; p = 0.270	Greater/lesser harm not proven

Table 18: 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** **Quantile of time to event (months) or MD** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
a. Probability provided if there is a statistically significant and relevant effect. b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u). AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; MD: mean difference; MDASI-MM: MD Anderson Symptom Inventory for multiple myeloma; NA: not achieved; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus		

2.5.2 Overall conclusion on added benefit

Table 19 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 19: Positive and negative effects from the assessment of elotuzumab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone

Positive effects	**Negative effects**
Mortality ▪ Overall survival indication of an added benefit – extent: “minor”	-
Serious/severe side effects ▪ AEs (CTCAE grade 3–4) ▫ Number of prior lines of treatment: 2–3 hint of lesser harm – extent: “major”	
The company’s dossier contains neither data on health-related quality of life nor adequate analyses on specific AEs.	
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events	

Overall, only positive effects with different certainty of results (indication or hint) were found for elotuzumab + pomalidomide + dexamethasone versus pomalidomide + dexamethasone in the outcome categories of mortality and side effects.

There was an indication of a minor added benefit for the outcome “overall survival”. In addition, there was a hint of lesser harm for the outcome “severe AEs (CTCAE grade 3–4)” in patients who had received 2 or 3 lines of treatment before enrolment.

Symptoms and complications of the underlying disease may have also been included in the analysis of AEs. Furthermore, there were no usable analyses on specific AEs. It is not assumed, however, that this calls into question the added benefit resulting from the outcome "overall survival".

In summary, there is an indication of a minor added benefit of elotuzumab + pomalidomide + dexamethasone versus 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 and have demonstrated disease progression on the last therapy.

The result of the assessment of the added benefit of elotuzumab + pomalidomide + dexamethasone in comparison with the ACT is summarized in Table 20.

Table 20: Elotuzumab – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Elotuzumab in combination with pomalidomide and dexamethasone for the treatment of relapsed and refractory multiple myeloma in adult patients 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	Indication of minor added benefit

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.

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

2.6 List of included studies

ELOQUENT-3

Bristol-Myers Squibb. An investigational immuno-therapy trial of pomalidomide and low-dose dexamethasone with or without elotuzumab to treat refractory and relapsed and refractory multiple myeloma (ELOQUENT-3): study details [online]. In: ClinicalTrials.gov. 03.06.2019 [Accessed: 16.10.2019]. URL: https://ClinicalTrials.gov/show/NCT02654132.

Bristol-Myers Squibb. Eine randomisierte Phase-2 Studie mit Pomalidomid / Dexamethason mit oder ohne Elotuzumab bei wiederkehrendem und refraktärem multiplen Myelom [online]. In: Deutsches Register Klinischer Studien. 31.10.2016 [Accessed: 16.10.2019]. URL: http://www.drks.de/DRKS00010601.

Bristol-Myers Squibb. An investigational immuno-therapy trial of pomalidomide and low-dose dexamethasone with or without elotuzumab to treat refractory and relapsed and refractory multiple myeloma (ELOQUENT-3): study results [online]. In: ClinicalTrials.gov. 03.06.2019 [Accessed: 16.10.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT02654132.

Bristol-Myers Squibb. An open label, randomized phase 2 trial of pomalidomide/dexamethasone with or without elotuzumab in relapsed and refractory multiple myeloma [online]. In: JAPIC Clinical Trials Information. 26.07.2017 [Accessed: 16.10.2019]. URL: https://www.clinicaltrials.jp/cti-user/trial/ShowDirect.jsp?japicId=JapicCTI-163245.

Bristol-Myers Squibb. An open label, randomized phase 2 trial of pomalidomide/dexamethasone with or without elotuzumab in relapsed and refractory multiple myeloma: study CA204125; final clinical study report [unpublished]. 2018.

Bristol-Myers Squibb. An open label, randomized phase 2 trial of pomalidomide/dexamethasone with or without elotuzumab in relapsed and refractory multiple myeloma: study CA204125; addendum 01 to final clinical study report [unpublished]. 2018.

Bristol-Myers Squibb. An open label, randomized phase 2 trial of pomalidomide/dexamethasone with or without elotuzumab in relapsed and refractory multiple myeloma: study CA204125; addendum 02 to final clinical study report [unpublished]. 2019.

Bristol-Myers Squibb. An open label, randomized phase 2 trial of pomalidomide/dexamethasone with or without elotuzumab in relapsed and refractory multiple myeloma: study CA204125; erratum to final clinical study report [unpublished]. 2019.

Bristol-Myers Squibb International. An open label, randomized phase 2 trial of pomalidomide/dexamethasone with or without elotuzumab in relapsed and refractory multiple myeloma [online]. In: EU Clinical Trials Register. [Accessed: 16.10.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-003282-19.

Dimopoulos MA, Dytfeld D, Grosicki S, Moreau P, Takezako N, Hori M et al. Elotuzumab plus pomalidomide and dexamethasone for multiple myeloma. N Engl J Med 2018; 379(19): 1811-1822.

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 5.0 [online]. 10.07.2017 [Accessed: 04.06.2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58.

3. European Medicines Agency. Empliciti: European public assessment report; variation EMEA/H/C/003967/II/0012 [online]. 25.07.2019 [Accessed: 23.10.2019]. URL: https://www.ema.europa.eu/documents/variation-report/empliciti-h-c-003967-ii-0012-epar-assessment-report-variation_en.pdf.

4. Wörmann B, Driessen C, Einsele H, Goldschmidt H, Gunsilius E, Kortüm M et al. Multiples Myelom [online]. In: Onkopedia Leitlinien. 05.2018 [Accessed: 22.10.2019]. URL: https://www.onkopedia.com/de/onkopedia/guidelines/multiples-myelom/@@guideline/html/index.html.

5. Moreau P, San Miguel J, Sonneveld P, Mateos MV, Zamagni E, Avet-Loiseau H et al. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017; 28(Suppl 4): iv52-iv61.

6. Bristol-Myers Squibb. Empliciti 300 mg/400 mg Pulver für ein Konzentrat zur Herstellung einer Infusionslösung: Fachinformation [online]. 08.2019 [Accessed: 23.10.2019]. URL: https://www.fachinfo.de/.

7. Celgene. IMNOVID Hartkapseln: Fachinformation [online]. 05.2019 [Accessed: 23.10.2019]. URL: https://www.fachinfo.de/.

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a19-80-elotuzumab-multiple-myeloma-benefit-assessment-according-to-35a-social-code-book-v.12599.html.