Elranatamab (multiple myeloma)

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

EXTRACT

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[1] Translation of Sections I 1 to I 6 of the dossier assessment *Elranatamab (multiples Myelom) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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

Patient and family involvement

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

IQWiG thanks the respondent and the plasmacytoma/multiple myeloma support group NRW (Plasmozytom/Multiples Myelom NRW) for participating in the written exchange and for their support. The respondent and the plasmacytoma/multiple myeloma support group NRW were not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
CD	cluster of differentiation
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PS	Propensity Score
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) has commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug elranatamab. 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 15 January 2024.

Research question

The aim of this report is to assess the added benefit of elranatamab compared with the appropriate comparator therapy (ACT) in adults with relapsed and refractory multiple myeloma who have received at least 3 prior therapies, including an immunomodulatory drug, a proteasome inhibitor, and an anti-cluster-of-differentiation 38 (CD38) antibody, and who have demonstrated disease progression on the last therapy.

The research question presented in Table 2 is derived from the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of elranatamab

Therapeutic indication	**ACT**[a]
Adults with relapsed and refractory multiple myeloma who have received at least 3 prior therapies, including an immunomodulatory drug, a proteasome inhibitor, and an anti-CD38 antibody, and have demonstrated disease progression on the last therapy	Individualized treatment[b, c,d] with a choice of: ▪ bortezomib monotherapy ▪ bortezomib + pegylated liposomal doxorubicin ▪ bortezomib + dexamethasone ▪ carfilzomib + lenalidomide and dexamethasone ▪ carfilzomib + dexamethasone ▪ daratumumab + lenalidomide + dexamethasone ▪ daratumumab + bortezomib + dexamethasone ▪ daratumumab monotherapy ▪ daratumumab + pomalidomide + dexamethasone ▪ elotuzumab + lenalidomide + dexamethasone ▪ elotuzumab + pomalidomide + dexamethasone ▪ isatuximab + pomalidomide + dexamethasone ▪ ixazomib + lenalidomide + dexamethasone ▪ lenalidomide + dexamethasone ▪ panobinostat + bortezomib and dexamethasone ▪ pomalidomide + bortezomib and dexamethasone ▪ pomalidomide + dexamethasone ▪ cyclophosphamide in combination with other antineoplastic drugs ▪ melphalan as monotherapy or in combination with prednisolone or prednisone ▪ doxorubicin as monotherapy or in combination with other antineoplastic drugs ▪ vincristine in combination with other antineoplastic drugs ▪ dexamethasone in combination with other antineoplastic drugs ▪ prednisolone in combination with other antineoplastic drugs ▪ prednisone in combination with other antineoplastic drugs ▪ best supportive care[e] taking into account prior therapies as well as the extent and duration of the response

a. Presented is the ACT specified by the G-BA.
b. High-dose chemotherapy with stem cell transplantation is presumed not to be an option for the patients at the time of their current treatment.
c. The special situation of refractory patients is presumably taken into account when choosing the ACT.
d. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study).
e. Best supportive care refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; CD: cluster of differentiation; G-BA: Federal Joint Committee

The company follows the ACT of an individualized treatment specified by the G-BA, while also pointing out that, in its view, further therapy options should be part of the ACT.

The assessment was conducted versus the ACT specified by the G-BA by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results

Concurring with the company's assessment, the check of completeness of the study pool did not identify any relevant randomized controlled trials (RCTs) for the direct comparison of elranatamab versus the ACT specified by the G-BA.

The company included the MagnetisMM-3 study in its benefit assessment as the best available evidence for elranatamab. The MagnetisMM-3 study is a single-arm study and does not allow for comparison versus the ACT specified by the G-BA.

Overall, the company has therefore presented no suitable data for deriving an added benefit in comparison with the ACT.

Results on added benefit

No suitable data in comparison with the ACT are available for the assessment of added benefit of elranatamab in the treatment of adults with relapsed and refractory multiple myeloma who have received at least 3 prior therapies, including an immunomodulatory drug, a proteasome inhibitor, and an anti-CD38 antibody, and who have demonstrated disease progression on the last therapy. There is no hint of an added benefit of elranatamab 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]

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

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Elranatamab – probability and extent of added benefit (multipage table)

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adults with relapsed and refractory multiple myeloma who have received at least 3 prior therapies, including an immunomodulatory drug, a proteasome inhibitor, and an anti-CD38 antibody, and have demonstrated disease progression on the last therapy	Individualized treatment[b, c,d] with a choice of: ▪ bortezomib monotherapy ▪ bortezomib + pegylated liposomal doxorubicin ▪ bortezomib + dexamethasone ▪ carfilzomib + lenalidomide and dexamethasone ▪ carfilzomib + dexamethasone ▪ daratumumab + lenalidomide + dexamethasone ▪ daratumumab + bortezomib + dexamethasone ▪ daratumumab monotherapy ▪ daratumumab + pomalidomide + dexamethasone ▪ elotuzumab + lenalidomide + dexamethasone ▪ elotuzumab + pomalidomide + dexamethasone ▪ isatuximab + pomalidomide + dexamethasone ▪ ixazomib + lenalidomide + dexamethasone ▪ lenalidomide + dexamethasone ▪ panobinostat + bortezomib and dexamethasone ▪ pomalidomide + bortezomib and dexamethasone ▪ pomalidomide + dexamethasone ▪ cyclophosphamide in combination with other antineoplastic drugs ▪ melphalan as monotherapy or in combination with prednisolone or prednisone ▪ doxorubicin as monotherapy or in combination with other antineoplastic drugs ▪ vincristine in combination with other antineoplastic drugs ▪ dexamethasone in combination with other antineoplastic drugs ▪ prednisolone in combination with other antineoplastic drugs ▪ prednisone in combination with other antineoplastic drugs ▪ best supportive care[e] taking into account prior therapies as well as the extent and duration of the response	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. High-dose chemotherapy with stem cell transplantation is presumed not to be an option for the patients at the time of their current treatment.
c. The special situation of refractory patients is presumably taken into account when choosing the ACT.
d. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study).
e. Best supportive care refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; CD: cluster of differentiation; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of elranatamab compared with the ACT in adults with relapsed and refractory multiple myeloma who have received at least 3 prior therapies, including an immunomodulatory drug, a proteasome inhibitor, and an anti-cluster-of-differentiation 38 (CD38) antibody, and who have demonstrated disease progression on the last therapy.

The research question presented in Table 4 is derived from the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of elranatamab

Therapeutic indication	**ACT**[a]
Adults with relapsed and refractory multiple myeloma who have received at least 3 prior therapies, including an immunomodulatory drug, a proteasome inhibitor, and an anti-CD38 antibody, and have demonstrated disease progression on the last therapy	Individualized treatment[b, c,d] with a choice of: ▪ bortezomib monotherapy ▪ bortezomib + pegylated liposomal doxorubicin ▪ bortezomib + dexamethasone ▪ carfilzomib + lenalidomide and dexamethasone ▪ carfilzomib + dexamethasone ▪ daratumumab + lenalidomide + dexamethasone ▪ daratumumab + bortezomib + dexamethasone ▪ daratumumab monotherapy ▪ daratumumab + pomalidomide + dexamethasone ▪ elotuzumab + lenalidomide + dexamethasone ▪ elotuzumab + pomalidomide + dexamethasone ▪ isatuximab + pomalidomide + dexamethasone ▪ ixazomib + lenalidomide + dexamethasone ▪ lenalidomide + dexamethasone ▪ panobinostat + bortezomib and dexamethasone ▪ pomalidomide + bortezomib and dexamethasone ▪ pomalidomide + dexamethasone ▪ cyclophosphamide in combination with other antineoplastic drugs ▪ melphalan as monotherapy or in combination with prednisolone or prednisone ▪ doxorubicin as monotherapy or in combination with other antineoplastic drugs ▪ vincristine in combination with other antineoplastic drugs ▪ dexamethasone in combination with other antineoplastic drugs ▪ prednisolone in combination with other antineoplastic drugs ▪ prednisone in combination with other antineoplastic drugs ▪ best supportive care[e] taking into account prior therapies as well as the extent and duration of the response

a. Presented is the ACT specified by the G-BA.
b. It is assumed that high-dose chemotherapy with stem cell transplantation is not an option for the patients at the time of their current treatment.
c. The special situation of refractory patients is presumably taken into account when choosing the ACT.
d. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study).
e. Best supportive care refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; CD: cluster of differentiation; G-BA: Federal Joint Committee

The company follows the ACT of an individualized treatment specified by the G-BA, while also pointing out that, in its view, further therapy options should be part of the ACT.

The assessment was conducted versus the ACT specified by the G-BA by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

I 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 lists on elranatamab (status: 16 November 2023)
- bibliographical literature search on elranatamab (last search on 16 November 2023)
- search in trial registries/trial results databases for studies on elranatamab (last search on 16 November 2023)
- search on the G-BA website for elranatamab (last search on 16 November 2023)

To check the completeness of the study pool:

- search in trial registries for studies on elranatamab (last search on 1 February 2024); for search strategies, see I Appendix A of the full dossier assessment

Direct comparison

No relevant RCTs for the direct comparison of elranatamab versus the ACT specified by the G-BA were identified by the check. This concurs with the company's assessment.

In Module 4 A, the company listed the ongoing RCT MagnetisMM-5 [3] in the company's list of studies in which RCTs that are conducted in whole or in part in the present therapeutic indication are to be mentioned. In the 3-arm MagnetisMM-5 study, elranatamab is being compared with elranatamab + daratumumab and daratumumab + pomalidomide + dexamethasone. Patients with relapsed or refractory multiple myeloma who have previously received at least 1 therapy including lenalidomide and a proteasome inhibitor are included. The company did not use the study for its benefit assessment because no study results are yet available. That is comprehensible. The study is expected to end in 2026. Based on the available study information, it cannot be assessed whether the study or a subpopulation would generally be relevant for a benefit assessment in the present therapeutic indication.

Further studies and evidence presented by the company

The company has conducted an information retrieval on further investigations with elranatamab and identified the single-arm MagnetisMM-3 study [4], on the basis of which elranatamab was approved. The company conducted no information retrieval on further investigations with the ACT.

The MagnetisMM-3 study is an ongoing, single-arm, open-label, multicentre study. This includes 187 adult patients with multiple myeloma who are refractory to at least one immunomodulatory drug, a proteasome inhibitor, and an anti-CD38 antibody, and who have

demonstrated disease progression on the last therapy. There are 2 subpopulations within the study. Patients in Cohort A were naive to B-cell maturation antigen (BCMA)-directed therapy, while patients in cohort B had already received BCMA-directed therapy.

Since the MagnetisMM-3 study alone does not allow a comparison with the ACT, the company is investigating the possibility of comparing data from different sources using propensity score (PS)-based methods. For this purpose, it formed an external control arm from the TherapyMonitor Multiple Myeloma (TM-MM) database [5]. From this database, the company extracted a cohort according to the inclusion and exclusion criteria of Cohort A of the MagnetisMM-3 study.

The company stated that no sufficient balance between Cohort A from the MagnetisMM-3 study and the cohort from the TM-MM database could be achieved by weighting using stabilised inverse probability of treatment weighting (sIPTW) in the relevant confounders. As a result, the distribution of PS in the two cohorts differs significantly. The initially planned comparison of the two cohorts could not be carried out in full.

The company included the MagnetisMM-3 study as the best available evidence for elranatamab in its benefit assessment and derived a hint of a non-quantifiable added benefit on the basis of this study.

The MagnetisMM-3 study is a single-arm study and does not allow for comparison versus the ACT specified by the G-BA.

Overall, the company has therefore presented no suitable data for deriving an added benefit in comparison with the ACT.

I 4 Results on added benefit

No suitable data in comparison with the ACT are available for the assessment of added benefit of elranatamab in the treatment of adults with relapsed and refractory multiple myeloma who have received at least 3 prior therapies, including an immunomodulatory drug, a proteasome inhibitor, and an anti-CD38 antibody, and who have demonstrated disease progression on the last therapy. There is no hint of an added benefit of elranatamab in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

The result of the assessment of the added benefit of elranatamab in comparison with the ACT is summarized in Table 5.

Table 5: Elranatamab – probability and extent of added benefit (multipage table)

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adults with relapsed and refractory multiple myeloma who have received at least 3 prior therapies, including an immunomodulatory drug, a proteasome inhibitor, and an anti-CD38 antibody, and have demonstrated disease progression on the last therapy	Individualized treatment[b, c,d] with a choice of: ▪ bortezomib monotherapy ▪ bortezomib + pegylated liposomal doxorubicin ▪ bortezomib + dexamethasone ▪ carfilzomib + lenalidomide and dexamethasone ▪ carfilzomib + dexamethasone ▪ daratumumab + lenalidomide + dexamethasone ▪ daratumumab + bortezomib + dexamethasone ▪ daratumumab monotherapy ▪ daratumumab + pomalidomide + dexamethasone ▪ elotuzumab + lenalidomide + dexamethasone ▪ elotuzumab + pomalidomide + dexamethasone ▪ isatuximab + pomalidomide + dexamethasone ▪ ixazomib + lenalidomide + dexamethasone ▪ lenalidomide + dexamethasone ▪ panobinostat + bortezomib and dexamethasone ▪ pomalidomide + bortezomib and dexamethasone ▪ pomalidomide + dexamethasone ▪ cyclophosphamide in combination with other antineoplastic drugs ▪ melphalan as monotherapy or in combination with prednisolone or prednisone ▪ doxorubicin as monotherapy or in combination with other antineoplastic drugs ▪ vincristine in combination with other antineoplastic drugs ▪ dexamethasone in combination with other antineoplastic drugs ▪ prednisolone in combination with other antineoplastic drugs ▪ prednisone in combination with other antineoplastic drugs ▪ best supportive care[e] taking into account prior therapies as well as the extent and duration of the response	Added benefit not proven

Table 5: Elranatamab – probability and extent of added benefit (multipage table)

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
a. Presented is the ACT specified by the G-BA. b. High-dose chemotherapy with stem cell transplantation is presumed not to be an option for the patients at the time of their current treatment. c. The special situation of refractory patients is presumably taken into account when choosing the ACT. d. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). e. Best supportive care refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. ACT: appropriate comparator therapy; CD: cluster of differentiation; G-BA: Federal Joint Committee		

The assessment described above deviates from that by the company, which derived a hint of a non-quantifiable added benefit.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

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