IQWiG Reports – Commission No. A22-100

Selinexor (multiple myeloma, ≥ 1 prior therapy) –

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

Extract

[1] Translation of Sections I 1 to I 6 of the dossier assessment *Selinexor (multiples Myelom ≥ 1 Vortherapie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 23 December 2022). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Selinexor (multiple myeloma, ≥ 1 prior therapy) – Benefit assessment according to §35a Social Code Book V

Commissioning agency
Federal Joint Committee

Commission awarded on
29 September 2022

Internal Commission No.
A22-100

Address of publisher
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

- Ingo Schmidt-Wolf, University Hospital Bonn, Germany

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 von Lier.

IQWiG thanks the respondent for participating in the written exchange about how he experienced the disease and its treatment and about the treatment goals. The respondent was not involved in the actual preparation of the dossier assessment.

IQWiG employees involved in the dossier assessment

- Anna-Katharina Barnert
- Christiane Balg
- Lars Beckmann
- Michaela Florina Kerekes
- Katrin Nink
- Annika Orland
- Min Ripoll
- Ulrike Seay

Keywords: Selinexor, Multiple Myeloma, Benefit Assessment, NCT03110562

Part I: Benefit assessment

I Table of contents

Page

I List of tables[2]

Page

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CHMP	Committee for Medicinal Products for Human Use
CIPN20	Chemotherapy-Induced Peripheral Neuropathy 20
CTCAE	Common Terminology Criteria for Adverse Events
DGHO	Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (German Society for Haematology and Medical Oncology)
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC	European Organisation for Research and Treatment of Cancer
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MMRM	mixed-effects model with repeated measures
PFS	progression-free survival
PRO	patient-reported outcome
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire-Core 30
RCT	randomized controlled trial
R-ISS	Revised International Staging System
ROW	rest of the world
RPSFTM	rank preserving structural failure time model
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
VAS	visual analogue scale

I 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 selinexor in combination with bortezomib and dexamethasone (hereinafter referred to as "selinexor + bortezomib + 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 29 September 2022.

Research question

The aim of this report is to assess the added benefit of selinexor + bortezomib + dexamethasone in comparison with the appropriate comparator therapy (ACT) in adult patients with multiple myeloma who have received at least one prior therapy.

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

Table 2: Research question of the benefit assessment of selinexor

Therapeutic indication	**ACT[a]**
Adult patients with multiple myeloma who have received at least one previous treatment[b, c]	▪ Bortezomib in combination with pegylated liposomal doxorubicin or ▪ **bortezomib in combination with dexamethasone** or ▪ lenalidomide 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 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 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. c. It is assumed that the special situation of refractory patients is taken into account when choosing the ACT. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

Following the G-BA's specification, the company selected bortezomib in combination with dexamethasone (bortezomib + dexamethasone) as ACT from the specified options.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) are used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

Study pool and study design

The BOSTON study was included in the benefit assessment.

The BOSTON study is a completed, active-controlled, open-label RCT comparing selinexor + bortezomib + dexamethasone versus treatment with bortezomib + dexamethasone.

The study included adult patients with relapsed and/or refractory multiple myeloma with 1 to 3 prior therapies. Patients had to have a general condition according to the Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 2 and must not have discontinued prior bortezomib treatment due to grade ≥ 3 toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE). In addition, at least 6 months had to have passed since the most recent bortezomib therapy before starting the study medication. Prior stem cell transplantation or ineligibility for stem cell therapy was not an inclusion criterion, but any autologous stem cell transplantation had to have taken place at least 1 month previously. According to the Summary of Product Characteristics (SPC) of bortezomib, prior stem cell transplantation or unsuitability for stem cell transplantation is a precondition for initiating treatment with bortezomib + dexamethasone. About 65% of the patients in the BOSTON study had not received prior stem cell transplantation. The company did not state whether stem cell transplantation was not suitable for these patients and whether this was also not a suitable treatment option at the time of the current therapy.

A total of 402 patients were randomized to the study arms: 195 patients to the intervention arm and 207 patients to the comparator arm.

Treatment with selinexor + bortezomib + dexamethasone was initially in a 3-week cycle. From the ninth cycle onwards, the treatment was administered in 5-week cycles. Treatment with bortezomib + dexamethasone in the comparator arm deviated from the specifications of the SPC of bortezomib in that bortezomib was not discontinued after the recommended maximum number of 8 cycles.

Treatment with the randomized study medication was discontinued, among other things, when disease progression or unacceptable toxicity occurred. In the event of disease progression and confirmation of progression by an independent committee, it was possible to switch from the comparator arm to treatment with selinexor (treatment switching). The company did not provide any further information on subsequent antineoplastic therapies.

The primary outcome was progression-free survival (PFS). Patient-relevant secondary outcomes were overall survival, morbidity, health-related quality of life and adverse events (AEs).

Data cut-offs

Analyses on 3 data cut-offs are available.

- 15 February 2021: data on mortality, morbidity, and health-related quality of life
- 22 March 2022: data on mortality
- 5 June 2022: data on side effects

Risk of bias and certainty of conclusions

The risk of bias across outcomes is rated as low for the BOSTON study. For the results on overall survival, the risk of bias is rated as high, since due to the lack of information on the subsequent therapies used, it cannot be assessed whether the patients in both treatment arms received guideline-compliant subsequent antineoplastic therapies. In addition, approximately 39% of patients in the comparator arm crossed over to treatment with selinexor + bortezomib + dexamethasone (n = 66 [32%]) or selinexor + dexamethasone (14 [7%]) in the sense of treatment switching. There is no information available regarding the times at which the patients switched treatment or reasons for the switch.

The risk of bias of the results on the outcomes of serious AEs (SAEs), severe AEs, as well as gastrointestinal disorders (severe AEs), peripheral neuropathy (severe AEs), cataract (severe AEs), and further specific AEs is rated as high. Even though the median treatment durations are comparable between the treatment arms, there are clear differences in the reasons for treatment discontinuation. At the data cut-off on 15 February 2021, 83 (43%) patients in the intervention arm had discontinued treatment prematurely due to disease progression, compared with 123 (60%) in the comparator arm. In contrast, 89 (46%) patients in the intervention arm discontinued treatment for other reasons (discontinuation by the patient, AE/toxicity, lost to follow-up, noncompliance, physician's decision, other), compared with 60 (29%) patients in the comparator arm. For the mentioned outcomes of the category of side effects, there are incomplete observations for various reasons due to the follow-up observation linked to the treatment duration and a possible association between outcome and reason for treatment discontinuation. The use of bortezomib beyond 8 cycles is not in compliance with the specifications in the SPC of bortezomib. Furthermore, it ultimately remains unclear from the information provided by the company whether autologous stem cell therapy was not suitable for the patients at the time of the current therapy. Due to the small proportion of patients pretreated with autologous stem cell therapy, the certainty of conclusions of the results is additionally reduced.

In this situation, only hints, e.g. of an added benefit, can therefore be derived on the basis of the BOSTON study.

Results

Overall survival

For the outcome of overall survival, no statistically significant difference between treatment groups was found. However, this result has a high risk of bias already due to the high proportion of patients with treatment switching from the comparator arm to the intervention arm and the missing data on subsequent therapies. Furthermore, there are uncertainties regarding the transferability of the results to the German health care context. In addition, there is a late crossing of the Kaplan-Meier curves for the total population. The observed effect modification by the characteristic of age might explain the crossing graphs. Without further information on the number of patients in the respective subgroup (age ≥ 65 years and age < 65 years) who switched from the comparator arm to treatment with selinexor and on the time points the treatment switches took place, the results on overall survival cannot be meaningfully interpreted.

In the overall assessment, the results for the outcome of overall survival are not considered to be meaningfully interpretable and are not used for deriving the added benefit. This results in no hint of an added benefit of selinexor + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone; an added benefit is therefore not proven.

Morbidity

Symptoms (EORTC QLQ-C30 and EORTC QLQ-CIPN20)

No suitable data are available for the outcomes on symptoms, recorded with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and the EORTC QLQ – Chemotherapy-Induced Peripheral Neuropathy 20 (CIPN20). This results in no hint of an added benefit of selinexor + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

No suitable data are available for the outcome of health status, recorded with the EQ-5D visual analogue scale (VAS). This results in no hint of an added benefit of selinexor + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

No suitable data are available for the outcome of health-related quality of life, recorded with the EORTC QLQ-C30 functional scales. This results in no hint of an added benefit of selinexor + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone; an added benefit is therefore not proven.

Side effects

SAEs and severe AEs

For the outcomes of SAEs and severe AEs, a statistically significant difference was found to the disadvantage of selinexor + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone. This results in a hint of greater harm of selinexor + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone for each of these outcomes.

Discontinuation due to AEs

No statistically significant difference was found between treatment groups for the outcome of discontinuation due to AEs. This results in no hint of an added benefit of selinexor + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone; an added benefit is therefore not proven.

Gastrointestinal disorders (severe AEs) and cataract (severe AEs)

For each of the outcomes of gastrointestinal disorders (severe AEs) and cataract (severe AEs), a statistically significant difference was found to the disadvantage of selinexor + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone. This results in a hint of greater harm of selinexor + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone for each of these outcomes.

Peripheral neuropathy (severe AEs)

No suitable data are available for the outcome of peripheral neuropathy (severe AEs). This results in no hint of greater or lesser harm from selinexor + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone; greater or lesser harm is therefore not proven.

Further specific AEs

Cardiac disorders (AEs), respiratory, thoracic and mediastinal disorders (SAEs), blood and lymphatic system disorders (severe AEs), infections and infestations (severe AEs), general disorders and administration site conditions (severe AEs), metabolism and nutrition disorders (severe AEs)

A statistically significant difference to the disadvantage of selinexor + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone was shown for each of the outcomes of respiratory, thoracic and mediastinal disorders (SAEs), blood and lymphatic system disorders (severe AEs), general disorders and administration site conditions (severe AEs) and metabolism and nutrition disorders (severe AEs). This results in a hint of greater harm of selinexor + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone for each of these outcomes.

For the outcome of infections and infestations (severe AEs), there is an effect modification by the characteristic of sex. For women, there is a hint of greater harm of selinexor + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone. For men, there is no hint of

greater or lesser harm of selinexor + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone; greater or lesser harm is therefore not proven for male patients.

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

Overall, this results in exclusively negative effects of selinexor + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone. All these negative effects are related to outcomes in the category of side effects and only refer to the shortened time period until 30 days after discontinuation of treatment.

Since no suitable data are available for the outcome categories of morbidity and health-related quality of life, and the results for the outcome of mortality cannot be meaningfully interpreted, it is not possible to weigh up the benefits and harms.

A meaningful interpretation of the results on overall survival is not possible in the present data situation. This also concerns the observed effect modification by age, which shows a disadvantage for patients < 65 years and an advantage for those ≥ 65 years of age. Neither added benefit nor lesser benefit can be derived on the basis of the data situation described.

In summary, added benefit of selinexor + bortezomib + dexamethasone in comparison with the ACT is not proven for adult patients with multiple myeloma who have received at least one prior therapy.

Table 3 shows a summary of the probability and extent of added benefit of selinexor + bortezomib + dexamethasone.

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

Table 3: Selinexor + bortezomib + dexamethasone – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with multiple myeloma who have received at least one previous treatment[b, c]	▪ Bortezomib in combination with pegylated liposomal doxorubicin or ▪ **bortezomib in combination with dexamethasone** or ▪ lenalidomide 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	Added benefit not proven

a. Presented is the 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 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.
c. It is assumed that the special situation of refractory patients is taken into account when choosing the ACT.

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

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

I 2 Research question

The aim of this report is to assess the added benefit of selinexor + bortezomib + dexamethasone in comparison with the ACT in adult patients with multiple myeloma who have received at least one prior therapy.

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

Table 4: Research question of the benefit assessment of selinexor

Therapeutic indication	**ACT**[a]
Adult patients with multiple myeloma who have received at least one previous treatment[b, c]	▪ Bortezomib in combination with pegylated liposomal doxorubicin or ▪ **bortezomib in combination with dexamethasone** or ▪ lenalidomide 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 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 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. c. It is assumed that the special situation of refractory patients is taken into account when choosing the ACT. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

Following the G-BA's specification, the company selected bortezomib in combination with dexamethasone (bortezomib + dexamethasone) as ACT from the specified options.

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

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 list on selinexor (status: 22 July 2022)
- bibliographical literature search on selinexor (last search on 22 July 2022)
- search in trial registries/trial results databases for studies on selinexor (last search on 26 July 2022)
- search on the G-BA website for selinexor (last search on 26 July 2022)

To check the completeness of the study pool:

- search in trial registries for studies on selinexor (last search on 11 October 2022); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant studies.

I 3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: selinexor + bortezomib + dexamethasone vs. bortezomib + dexamethasone

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
BOSTON	Yes	No	Yes[d]	Yes [3]	Yes [4-6]	Yes [7-14]

a. Study for which the company was sponsor.
b. Citation of the trial registry entries and, if available, of the reports on 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. Karyopharm Therapeutics Inc. was sponsor of the study. The marketing authorization holder in the EU for the drug under assessment (selinexor) is Stemline Therapeutics B.V.

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

I 3.2 Study characteristics

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

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
BOSTON	RCT, open-label, parallel	Adults (≥ 18 years) with relapsed and/or refractory multiple myeloma with ▪ 1 to 3 prior therapies[b] ▪ disease progression on or after most recent regimen ▪ ECOG PS ≤ 2	Selinexor + bortezomib + dexamethasone (N = 195) Bortezomib + dexamethasone (N = 207)[c]	Screening: ≤ 28 days before initiation of study medication Treatment: until disease progression[c], unacceptable toxicity, consent withdrawal, death, or end of study Observation: outcome-specific[d], consent withdrawal, lost to follow-up, death, or end of study (maximum of 5 years after end of treatment)	123 centres in 21 countries: Australia, Austria, Belgium, Bulgaria, Canada, Czech Republic, France, Germany, Greece, Hungary, India, Israel, Italy, Poland, Romania, Russia, Serbia, Spain, Ukraine, United Kingdom, USA 6/2017–6/2022 Data cut-offs: ▪ Interim analysis: 21 January 2019 ▪ Primary analysis: 18 February 2020 ▪ Final efficacy analysis: 15 February 2021 ▪ Supplementary analysis on overall survival[e]: 22 March 2022 ▪ Final safety analysis: 5 June 2022	Primary: PFS[f] Secondary: overall survival, morbidity, health-related quality of life, 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. Induction therapy followed by stem cell transplant and consolidation or maintenance therapy was considered as one prior therapy.
c. Patients with disease progression could switch to treatment with selinexor + bortezomib + dexamethasone or selinexor + dexamethasone, depending on whether or not bortezomib was tolerated.
d. Outcome-specific information is provided in Table 8.
e. Data cut-off requested by EMA.
f. With Amendment 3 to the study protocol (17 August 2018), the previous primary outcomes of PFS and ORR were changed to PFS as the only primary outcome.

AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EMA: European Medicines Agency; N: number of randomized patients; ORR: overall response rate; PFS: progression-free survival; RCT: randomized controlled trial; vs.: versus

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

Study	Intervention	Comparison
BOSTON	Selinexor 100 mg[a] orally: ▪ per cycle: days 1, 8, 15, 22 and 29 + bortezomib 1.3 mg/m² BSA SC: ▪ per cycle: days 1, 8, 15 and 22 + dexamethasone 20 mg orally: ▪ per cycle: days 1, 2, 8, 9, 15, 16, 22, 23, 29 and 30 One cycle has 5 weeks	Bortezomib 1.3 mg/m² BSA SC: ▪ cycles 1–8: days 1, 4, 8 and 11 ▪ from cycle 9[b]: days 1, 8, 15 and 22 + dexamethasone 20 mg orally: ▪ cycles 1–8: days 1, 2, 4, 5, 8, 9, 11 and 12 ▪ from cycle 9[b]: days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 One cycle has 3 weeks (cycles 1–8) or 5 weeks (from cycle 9)
	Treatment adjustments ▪ Dose escalation (not in compliance with SPC) of selinexor combination from cycle 3 if a PR was not achieved within the first 2 cycles, the current dose level was tolerated, and no AEs (CTCAE grade >2) had occurred by the time of dose escalation: ▫ selinexor 60 mg orally: days 1, 3, 8, 10, 15, 17, 22, 24, 29 and 31 ▫ bortezomib 1.3 mg/m² BSA SC: days 1, 3, 8, 10, 15, 17, 22, 24, 29 and 31 ▫ dexamethasone: 20 mg orally: on same day as selinexor ▪ Dose reduction due to toxicity: ▫ selinexor: according to the SPC ▫ bortezomib (in the event of peripheral neuropathy to 1.3 mg/m² BSA once a week, otherwise according to the SPC) ▫ dexamethasone (to a minimum dose of 10 to 12 mg twice a week) **Permitted pretreatment** ▪ prior treatment with bortezomib or other PI, provided all of the following criteria are met: ▫ best response achieved with prior bortezomib ≥ PR and with the last PI therapy (alone or in combination) ≥ PR ▫ no discontinuation of bortezomib treatment due to grade ≥ 3 toxicity ▫ ≥ 6-month PI-treatment-free interval prior to initiation of study medication ▪ glucocorticoids ≤ 2 weeks prior to initiation of study medication **Non-permitted pretreatment** ▪ autologous stem cell transplantation < 1 month or allogeneic stem cell transplantation < 4 months prior to initiation of study medication ▪ radiation[c], chemotherapy, immunotherapy or any other anticancer therapy ≤ 2 weeks prior to initiation of study medication	

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

Study	Intervention	Comparison
	Permitted concomitant treatment ▪ required: 5-HT3 antagonists ▪ all other medically necessary treatments, including: ▫ proton pump inhibitors, anti-hypertensives and glucose-lowering drugs ▫ anti-infectives ▫ red blood cell or platelet transfusion, anticoagulants, antianaemics (erythropoietin, darbepoetin), growth factors (e.g. G-CFS) and platelet stimulators ▫ palliative radiotherapy to non-target lesions (interruption of study treatment for ≥ 1 day before and ≥ 1 day after radiation) ▫ paracetamol or paracetamol-containing products[d] **Non-permitted concomitant treatment** ▪ other anticancer treatment ▪ for selinexor: GSH-, S-adenosylmethionine-, or N-acetylcysteine-containing products ▪ for bortezomib and dexamethasone: according to local SPCs	

a. In no case may the selinexor dose exceed 70 mg/m² BSA.
b. Administration of bortezomib + dexamethasone beyond 8 cycles is not in compliance with the European approval [15], but with the US approval [16].
c. Localized radiation to a single site at least 1 week before initiation of study medication is permitted.
d. On the day of selinexor administration: ≤ 1 g/day allowed.

5-HT3: 5-hydroxytryptamine type 3; BSA: body surface area; G-CSF: granulocyte colony-stimulating factor; GSH: glutathione S-transferase; PI: proteasome inhibitor; PR: partial response; RCT: randomized controlled trial; SC: subcutaneous

The BOSTON study is a completed, active-controlled, open-label RCT comparing selinexor + bortezomib + dexamethasone versus treatment with bortezomib + dexamethasone.

The study included adult patients with relapsed and/or refractory multiple myeloma with 1 to 3 prior therapies. Patients had to have a general condition according to ECOG PS of 0 to 2 and must not have discontinued prior bortezomib treatment due to grade ≥ 3 toxicity according to CTCAE. In addition, at least 6 months had to have passed since the most recent bortezomib therapy before starting the study medication. Prior stem cell transplantation or ineligibility for stem cell therapy was not an inclusion criterion, but any autologous stem cell transplantation had to have taken place at least 1 month previously. According to the SPC of bortezomib [15], prior stem cell transplantation or unsuitability for stem cell transplantation is a precondition for initiating treatment with bortezomib + dexamethasone. About 65% of the patients in the BOSTON study had not received prior stem cell transplantation. The company did not state whether stem cell transplantation was not suitable for these patients and whether this was also not a suitable treatment option at the time of the current therapy.

Randomization of the patients was stratified by Revised International Staging System (R-ISS) stage at screening (I/II versus III), the number of prior lines of treatment (1 versus > 1) and prior proteasome inhibitor therapies (no versus yes). A total of 402 patients were randomized to the study arms: 195 patients to the intervention arm and 207 patients to the comparator arm.

Treatment with selinexor + bortezomib + dexamethasone was in 5-week cycles, largely in compliance with the SPC [17]. Selinexor dose escalation in the event of insufficient response after 2 cycles of therapy, as stipulated in the study protocol, does not correspond to the specifications of the SPC. However, according to the company, this only affected about 5% of the patients in the intervention arm.

Treatment with bortezomib + dexamethasone in the comparator arm was initially in a 3-week cycle. From the ninth cycle onwards, the treatment was administered in 5-week cycles. The treatment deviated from the specifications of the SPC of bortezomib [15] in that bortezomib was not discontinued after the recommended maximum number of 8 cycles.

Patients in both study arms were required to receive 5-HT3 antagonists unless contraindicated. The company described in Module 4 A of its dossier that about 88% of patients in the selinexor arm were treated with 5-HT3 antagonists, but only about 36% of patients in the comparator arm. The company did not describe why the proportions of prophylactic therapy with 5-HT3 antagonists differed greatly between the arms. However, it cannot be assumed that this is solely due to the presence of contraindications. A recommendation for the administration of the 5-HT3 antagonists can be found in the SPC of selinexor, but there is no such recommendation in the SPC of bortezomib. Furthermore, since the emetogenic potential of bortezomib is considered low [18], a systematic undersupply of patients in the comparator arm is not assumed in the present case.

Treatment with the randomized study medication was discontinued, among other things, when disease progression or unacceptable toxicity occurred. In the event of disease progression, it was possible to switch from the comparator arm to treatment with selinexor (treatment switching) if the progression was confirmed by an independent committee. Switching to the triple combination of selinexor + bortezomib + dexamethasone was possible if bortezomib was tolerated by the patients. Patients who did not tolerate bortezomib therapy could switch to the dual combination of selinexor + dexamethasone. The company did not provide any further information on subsequent antineoplastic therapies.

The primary outcome was PFS. Patient-relevant secondary outcomes were overall survival, morbidity, health-related quality of life and AEs.

Data cut-offs

A total of 5 data cut-offs are available for the BOSTON study. In the dossier, the company presented analyses on 3 data cut-offs. Originally, 2 interim analyses were planned: The first interim analysis was planned after reaching about 30% or 81 PFS events for a possibly necessary adjustment of sample size planning. This analysis was performed on 21 January 2019 after reaching 113 PFS events with no resulting adjustments. A second interim analysis was planned after reaching about 201 PFS events (about 75% of planned events). Contrary to the original planning, this analysis now represents the final efficacy data cut-off (data cut-off on 18 February 2020).

At the request of the Committee for Medicinal Products for Human Use (CHMP), the company also conducted analyses for the data-off on 15 February 2021 for the outcomes of PFS, duration of response, objective response rate, overall survival, and AEs. In the dossier, the company additionally presented post hoc data on patient-reported outcomes (PROs) for this data cut-off.

For overall survival, results are available for the data cut-off of 22 March 2022, which was requested by the European Medicines Agency (EMA) as part of the marketing authorization procedure (third CHMP request for supplementary information).

In the dossier, results on side effects are available for the data cut-off on 5 June 2022. This analysis was not prespecified and, according to the company, was carried out by the company at the end of the study. In the dossier, the company thus presented results for a total of 3 data cut-offs:

- 15 February 2021: data on mortality, morbidity, and health-related quality of life
- 22 March 2022: data on mortality
- 5 June 2022: data on side effects

The company did not provide the results of the first 2 data cut-offs (21 January 2019 and 18 February 2020). It justified this by stating that no further gain in knowledge could be derived from this compared with the later data cut-offs.

The company did not explain why it presented data for 3 different data cut-offs and not for one joint data cut-off (for example, for the last mortality analysis from 22 March 2022). For the outcomes on morbidity and health-related quality of life, the company presented only data of the data cut-off from 15 February 2021. Patient-reported outcomes on morbidity and health-related quality of life were recorded until the end of treatment. At the data cut-off of 15 February 2021, 21 patients in the intervention arm and 16 patients in the comparator arm were still under treatment. Due to this small number, it is not expected that the submission of results on later data cut-offs would notably change the data situation for the PROs. However, it would be possible for the company to submit analyses for the data cut-off of 22 March 2022.

As there was only one patient in each study arm between the data cut-off of 22 March 2022 and the final safety data cut-off of 5 June 2022, the analyses of the AE outcomes for the data cut-off of 6 May 2022 are used for these outcomes despite the lack of information regarding the reason for the data cut-off.

Uncertainties of the BOSTON study

Number of patients with stem cell transplantation

In the BOSTON study, the proportion of patients with prior stem cell transplantation was about 35%. The company did not provide any information on whether the stem cell transplantations were autologous or allogeneic. According to the S3 guideline on multiple myeloma, autologous stem cell therapy should be offered to all transplant-eligible patients, both in the first-line setting

and in relapse [19]. A proportion of only about 1 third of patients with stem cell transplantation thus appears low with regard to the German health care context. The limited transferability to the German health care context resulting from this was most recently discussed in the benefit assessment of daratumumab [20].

Taking into account that autologous stem cell transplantation is part of the standard therapy in multiple myeloma in most countries, the EMA also considers the proportion of patients with prior stem cell transplantation in the BOSTON study to be relatively low.

As described, the company did not provide any additional information on whether high-dose chemotherapy with stem cell therapy was a treatment option for the patients at the time of the start of the study. Since the suitability of high-dose chemotherapy with stem cell therapy is weighed on the basis of individual factors and should be offered to all patients who are candidates for autologous stem cell transplantation, including relapsed patients, it remains open whether there are also patients in the study population for whom stem cell therapy would have been an adequate treatment option at the time of the current therapy.

Number of bortezomib cycles

According to the SPC of bortezomib [15], patients achieving a response or a stable disease after 4 cycles of therapy with bortezomib + dexamethasone can continue to receive the same combination for a maximum of 4 additional cycles. In the comparator arm of the BOSTON study, treatment with bortezomib + dexamethasone could be administered for more than 8 cycles. In addition, after the eighth cycle, the company extended the cycle length from 3 to 5 weeks. Administration beyond 8 cycles and adjustment to a 5-week cycle is in compliance with US approval [16]. The company did not provide any information on the proportion of patients in the BOSTON study who were actually treated with bortezomib beyond the eighth cycle.

The current S3 guideline generally recommends continuation of therapy until disease progression, depending on the initial response, tolerability, toxicity and the patient's wishes. It does not make a recommendation specifically for bortezomib-containing treatment [19]. The guideline by the German Society for Haematology and Medical Oncology (DGHO) recommends treating patients with bortezomib up to 2 cycles after the best response [21].

If tolerated, continuation of bortezomib therapy beyond 8 cycles thus appears possible in principle, but there is no clear recommendation to extend the cycle length in accordance with the US approval. As the company did not provide any information on the number of patients who received bortezomib beyond the 8 cycles, the existing uncertainties are taken into account in the certainty of conclusions.

Treatment switching

At the data cut-off of 22 March 2022, approximately 32% (N = 66) of patients from the comparator arm had switched to treatment with selinexor + bortezomib + dexamethasone and

approximately 7% (N = 14) had switched to selinexor + dexamethasone. This treatment switching is taken into account in the assessment of the risk of bias at outcome level.

Uncertainties do not lead to study exclusion

Overall, the uncertainties described do not lead to the exclusion of the study from the benefit assessment, but are taken into account when assessing the certainty of conclusions of the results and lead to a limitation of the certainty of conclusions (see Section I 4.2).

Planned duration of follow-up observation

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

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

Study **Outcome category** **Outcome**	**Planned follow-up observation**
BOSTON	
Mortality	
Overall survival	Until death, maximum of up to 5 years after end of treatment
Morbidity	
Symptoms/health status (EORTC QLQ-C30 symptom scales, EORTC QLQ-CIPN20, EQ-5D VAS)	Until the last dose of the study medication
Health-related quality of life (EORTC QLQ-C30)	Until the last dose of the study medication
Side effects	
All outcomes in the category of side effects	Up to 30 days after the last dose of the study medication or until initiation of a new anti-myeloma therapy (including crossover)
EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-CIPN20: Quality of Life Questionnaire – Chemotherapy-Induced Peripheral Neuropathy 20; RCT: randomized controlled trial; VAS: visual analogue scale	

The observation periods for the outcomes of morbidity, health-related quality of life and side effects were systematically shortened because they were recorded only for the time period of treatment with the study medication (plus 30 days for side effects). Drawing a reliable conclusion on the total study period or the time to patient death, however, would require surveying these outcomes for the total period, as was done for survival.

Characteristics of the study population

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

Table 9: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: selinexor + bortezomib + dexamethasone vs. bortezomib + dexamethasone (multipage table)

Study Characteristic Category	Selinexor + bortezomib + dexamethasone N[a] = 195	Bortezomib + dexamethasone N[a] = 207
BOSTON		
Age [years], mean (SD)	65 (10)	67 (9)
Sex [F/M], %	41/59	44/56
Family origin		
Asian	25 (13)	25 (12)
African	4 (2)	7 (3)
European	161 (83)	165 (80)
Other	0 (0)	1 (< 1)
Missing data	5 (3)	9 (4)
ECOG PS, n (%)		
0	69 (35)	77 (37)
1	106 (54)	114 (55)
2	20 (10)	16 (8)
R-ISS stage, n (%)		
I	56 (29)	52 (25)
II	117 (60)	125 (60)
III	12 (6)	16 (8)
Not available	10 (5)	14 (7)
Disease duration: time between first diagnosis and randomization [years]		
Mean (SD)	4.5 (3.3)	4.4 (3.3)
Median (min; max)	3.8 (0.4; 23.0)	3.6 (0.4; 22.0)
Type of myeloma at diagnosis, n (%)		
IgG	111 (57)	127 (61)
IgA	39 (20)	35 (17)
IgD	1 (1)	1 (< 1)
IgE	0 (0)	0 (0)
IgM	1 (1)	2 (1)
None	0 (0)	0 (0)
Missing	43 (22)	42 (20)
High-risk chromosomal abnormalities (baseline or initial diagnosis), n (%)		
del(17p)/p53	21 (11)	16 (8)
t(14;16)	7 (4)	11 (5)
t(4;14)	22 (11)	28 (14)
1q21	80 (41)	71 (34)
del(17p)/p53 or t(14;16) or t(4;14) or 1q21	97 (50)	95 (46)

Table 9: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: selinexor + bortezomib + dexamethasone vs. bortezomib + dexamethasone (multipage table)

Study Characteristic Category	**Selinexor + bortezomib + dexamethasone N[a] = 195**	**Bortezomib + dexamethasone N[a] = 207**
Prior therapies, n (%)		
Number of prior therapies, n (%)		
1	99 (51)	99 (48)
2	65 (33)	64 (31)
3	31 (16)	44 (21)
Prior stem cell transplant	76 (39)	63 (30)
Prior anti-myeloma radiotherapy	30 (15)	41 (20)
Prior anti-myeloma surgery	11 (6)	14 (7)
Prior anti-myeloma therapy, n (%)		
Bortezomib	134 (69)	145 (70)
Carfilzomib	20 (10)	21 (10)
Ixazomib	6 (3)	3 (1)
Daratumumab	11 (6)	6 (3)
Lenalidomide	77 (39)	77 (37)
Pomalidomide	11 (6)	7 (3)
Refractory to prior therapy, n (%)		
Bortezomib	18 (9)	29 (14)
Carfilzomib	5 (3)	5 (2)
Ixazomib	2 (1)	1 (< 1)
Daratumumab	10 (5)	6 (3)
Lenalidomide	53 (27)	53 (26)
Pomalidomide	10 (5)	6 (3)
Thalidomide	24 (12)	34 (16)
Treatment discontinuation[b] at data cut-off 15 Feb 2021, n (%)[c, d]	174 (89)	188 (92)
Treatment discontinuation[b] at data cut-off 22 Mar 2022, n (%)	ND	ND
Treatment discontinuation[b] at data cut-off 5 Jun 2022, n (%)[c, e]	195 (100)	204 (100)
Study discontinuation at data cut-off 15 Feb 2021, n (%)[c, f]	122 (63)	126 (62)
Study discontinuation at data cut-off 22 Mar 2022, n (%)[g]	ND	ND
Study discontinuation at data cut-off 5 Jun 2022, n (%)[c, h]	195 (100)	204 (100)

Table 9: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: selinexor + bortezomib + dexamethasone vs. bortezomib + dexamethasone (multipage table)

Study Characteristic Category	Selinexor + bortezomib + dexamethasone N[a] = 195	Bortezomib + dexamethasone N[a] = 207

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. It is unclear whether the data refer to the discontinuation of all or of any of the drug components.
c. These figures refer to the safety population (195 vs. 204 patients).
d. Common reasons for treatment discontinuation in the intervention arm vs. the control arm were disease progression (39% vs. 58%), discontinuation by patient (19% vs. 10%), and AE/toxicity (17% vs. 13%).
e. Common reasons for treatment discontinuation in the intervention arm vs. the control arm were disease progression (43% vs. 60%), discontinuation by patient (19% vs. 11%), and AE/toxicity (17% vs. 13%).
f. Common reasons for study discontinuation in the intervention arm vs. the control arm were death (35% vs. 39%), discontinuation by patient (20% vs. 19%), and lost to follow-up (6% vs. 3%).
g. According to the EPAR, 194 (99%) vs. 206 (99%) patients in the intervention arm vs. the control arm had discontinued the study at the data cut-off. Common reasons for study discontinuation were death (38% vs. 40%), discontinuation by patient (20% vs. 21%), and lost to follow-up (7% vs. 4%).
h. Common reasons for study discontinuation in the intervention arm vs. the control arm were death (38% vs. 40%), discontinuation by patient (20% vs. 20%), termination of the study by sponsor (30% vs. 33%).

ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; Ig: immunoglobulin; ISS: international staging system; M: male; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; R-ISS: Revised International Staging System; SD: standard deviation

The patient characteristics were largely balanced between the study arms. The mean age of the patients was about 66 years and the proportion of female patients was slightly lower than the proportion of male patients in both arms. According to the inclusion criteria, all patients had received at least one prior anti-multiple myeloma regimen before study inclusion. Approximately 70% of the patients had already been treated with bortezomib in prior lines of treatment. About 35% had received prior stem cell transplantation (see Section I 3.2).

The number of treatment and study discontinuations are comparable in both arms at the respective data cut-offs.

Information on the course of the study

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

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

Study **Duration of the study phase** **Outcome category**	**Selinexor + bortezomib + dexamethasone** **N = 195**	**Bortezomib + dexamethasone** **N = 207**
BOSTON		
Data cut-off 22 March 2022		
Treatment duration [months]		
Median [min; max]	ND	ND
Mean (SD)	ND	ND
Observation period [months]		
Overall survival[a]		
Median [95% CI]	33.6 [32.3; 35.2][b]	33.8 [32.9; 35.7][b]
Mean (SD)	ND	ND
Data cut-off 15 February 2021		
Treatment duration [months][b]		
Median [min; max]	6.8 [0.3; 39.2]	7.2 [0.2; 39.7]
Mean (SD)	10.9 (10.1)	10.1 (9.0)
Observation period [months]		
Morbidity, health-related quality of life[c]		
EQ-5D	ND	ND
EORTC QLQ-C30	ND	ND
EORTC-QLQ-CIPN20	ND	ND
Data cut-off 5 June 2022		
Treatment duration [months][b]		
Median [min; max]	6.8 [0.3; 47.7]	7.2 [0.2; 45.9]
Mean (SD)	11.5 (11.5)	10.5 (10.0)
Observation period [months]		
Side effects	ND	ND

a. The observation period is calculated on the basis of the observed time until censoring of all non-deceased patients.
b. The data on the median observation period for overall survival was taken from the EPAR.
c. These data refer to the safety population (195 vs. 204 patients).
d. Patient-reported outcomes were recorded until the end of randomized treatment.

CI: confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-CIPN20: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Chemotherapy-Induced Peripheral Neuropathy 20; max: maximum; min: minimum; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

The observation periods are comparable between the intervention arm and the comparator arm. The company did not provide any information on the observation period of the PROs of morbidity and health-related quality of life as well as side effects. The observation period of

these outcomes was linked to the treatment duration, so that the observation periods are notably shorter compared with overall survival. For these outcomes, conclusions can therefore be drawn only regarding the period under treatment (plus 30 days for side effects).

Information on subsequent therapies

According to the information in the study documents, the subsequent therapies administered after the study had to be recorded at regular intervals. In its dossier, the company did not present corresponding analyses of which subsequent therapies the patients in the intervention arm or in the comparator arm had received. However, the company itself stated in Module 4 A that the subsequent therapies have an essential influence on overall survival and that almost every patient in the present therapeutic indication receives subsequent therapy.

The results of the outcome of overall survival are profoundly influenced by the subsequent antineoplastic therapies used after disease progression or relapse. The use of adequate subsequent therapies is thus of great importance for the assessment of the results on overall survival. For the BOSTON study, it is not possible to assess whether the patients in both treatment arms received guideline-compliant subsequent therapy due to the lack of information on the subsequent therapies used. This is taken into account when assessing the risk of bias for the results of the outcome of overall survival (see Section I 4.2).

Risk of bias across outcomes (study level)

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

Table 11: Risk of bias across outcomes (study level) – RCT, direct comparison: selinexor + bortezomib + dexamethasone vs. bortezomib + 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			
BOSTON	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes is rated as low for the BOSTON study.

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

Transferability of the study results to the German health care context

The company described that transferability of the results of the BOSTON study to the German health care context was limited, which was shown by effect modifications, caused by the health care context, in various outcomes, especially in overall survival. It described an effect modification for the outcome of overall survival by the characteristic of region for a subgroup formed post hoc, which included the countries considered by the company to correspond to the German health care context (Austria, Belgium, France, Italy, Spain, Czech Republic, Greece, Hungary, Poland, Bulgaria, Romania, Great Britain, USA and Canada [EU/GB/NA] versus Australia, Israel, India, Russia, Serbia, Ukraine [rest of the world, ROW]). For example, the company attributed an increased number of deaths in India to a different health care structure compared with Germany. In particular, it considered the results for the EU/GB/NA subgroup to be representative for the German health care context. In total, 255 patients (63.4%) in the EU/GB/NA region had been treated in countries that provided health care comparable to the one in Germany, according to the company.

The company did not provide any further information on the transferability of the study results to the German health care context.

In agreement with the company, the transferability of the results of the BOSTON study to the German health care context is assessed as limited. However, the subgroup formed post hoc is not suitable to represent the German health care context. The prespecified regional subgroup of region 2 (Australia, Austria, Belgium, France, Germany, Israel, Italy, Spain, Great Britain) appears to correspond more closely to the German health care context than the EU/GB/NA subgroup formed post hoc. No effect modification can be derived for overall survival from the prespecified subgroup analyses on regions.

The uncertainties described above regarding the transferability of the study results in the present data situation are taken into account in the interpretation of the results.

I 4 Results on added benefit

I 4.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - symptoms measured with the EORTC QLQ-C30 and EORTC QLQ-CIPN20 symptom scales
  - health status recorded with the EQ-5D VAS
- Health-related quality of life
  - health-related quality of life measured with the EORTC QLQ-C30 functional scales
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - gastrointestinal disorders (System Organ Class [SOC], severe AEs)
  - peripheral neuropathy (Preferred Term [PT], severe AEs)
  - cataract (PT, severe AEs)
  - further specific AEs, if any

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

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

Table 12: Matrix of outcomes – RCT, direct comparison: selinexor + bortezomib + dexamethasone vs. bortezomib + dexamethasone

Study	Outcomes										
	Overall survival	Symptoms (EORTC QLQ-C30 and EORTC QLQ-CIPN20)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Gastrointestinal disorders (SOC, severe AEs[a])	Peripheral neuropathy (PT, severe AEs[a])	Cataract (PT, severe AEs[a])	Further specific AEs[a, b]
BOSTON	Yes	No[c]	No[c]	No[c]	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. The following events are considered (coded according to MedDRA): "cardiac disorders" (SOC, AEs), "respiratory, thoracic and mediastinal disorders" (SOC, SAEs), "blood and lymphatic system disorders" (SOC, severe AES), "infections and infestations" (SOC, severe AEs), "general disorders and administration site conditions" (SOC, severe AEs) and "metabolism and nutrition disorders" (SOC, severe AEs).
c. No suitable data available; see body of text below for reasons.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer-Core 30; EORTC QLQ-CIPN20: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Chemotherapy-Induced Peripheral Neuropathy 20; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Analyses of the company on the patient-reported outcomes of symptoms (EORTC QLQ-C30 and EORTC QLQ-CIPN 20), health status (EQ-5D VAS) and health-related quality of life (EORTC QLQ-C30 are not suitable

In Module 4 A, the company presented responder analyses for the symptoms and health-related quality of life outcomes (recorded with the EORTC QLQ-C30 and the EORTC QLQ-CIPN20) as well as the outcome of health status (recorded with the EQ-5D VAS). In Module 4 A, they were operationalized as "time to first deterioration" (from study start to a subsequent recording of PROs) by ≥ 15 points each (respective scale range of 0 to 100). However, the early benefit assessment procedure requires analyses at a response threshold of 10 points for the EORTC QLQ-C30 and its additional modules [22].

In addition, the company presented analyses of the continuous data on the weekly rate of change using a linear mixed effects model (which corresponds to a random coefficients model), in which a linear adjustment is made and the difference in rates is used as the effect measure. In contrast to a mixed-effects model with repeated measures (MMRM), this model can take different recording time points into account.

Both operationalizations, responder analyses analysed as time to first deterioration as well as the analysis of continuous data, are in principle suitable to allow drawing conclusions on the added. In the present data situation, however, the analyses presented are considered unsuitable, irrespective of the question of the response threshold. This is justified below:

In the BOSTON study, the treatment regimens differed between the study arms: Selinexor + bortezomib + dexamethasone was administered in a 5-week cycle for the entire duration of the study, while the cycle length in the comparator arm was 3 weeks for the first 8 cycles. PROs were recorded on the first day of each cycle. In the intervention arm, recording thus took place every 5 weeks. For patients in the comparator arm, however, recording took place every 3 weeks. From the ninth cycle onwards, the treatment regimen and thus also the recording of PROs in the comparator arm was changed to a 5-week cycle, analogous to the intervention arm (see Table 13).

Table 13: Recording time points of the PROs in the study arms

Treatment arms	**Recording time points (weeks)**																	
Selinexor + bortezomib + dexamethasone	0		5			10		15		20			25		30		35	…
Bortezomib + dexamethasone	0	3		6	9		12	15	18		21	24		29		34		…

The company's approach of performing the recording on the first day of each cycle, regardless of cycle length, is appropriate because by doing so, the company avoided performing recordings at different time points within a cycle and thereby reduced potential bias caused by this factor. However, the different cycle lengths between the intervention arm and the comparator arm over the first 8 cycles resulted in an increased number of recording time points in the comparator arm: Up to week 21, there were 4 recording time points in the intervention arm, and 7 recording time points in the comparator arm. This can potentially lead to more frequent observations of a deterioration in the study arm with more recordings (comparator arm) than in the study arm with fewer recordings (intervention arm).

The Kaplan-Meier curves show that, for most scales, the majority of events occurred early, so that these events occurred predominantly in the period of the different frequencies of recording (in the first 8 cycles). For this reason, the analyses presented cannot be interpreted on the basis of the information available.

In the present situation with different cycle lengths, there is no optimal analysis strategy, because, on the one hand, the recording at the beginning of each cycle is appropriate in both arms, but, on the other, this leads to the described problem of the different number of recordings. Therefore, additional analyses are required. One possibility would be to consider only the recordings that took place at the same time points for the period of the first 8 cycles for the

responder analyses, for example. In the present constellation, however, this would mean that only the recording at week 15 would be included in the analysis, leaving the vast majority of recordings unconsidered. In the present situation, it therefore seems appropriate to include all the recording time points that are no more than one week apart (see Table 14). This results in an equal number of recordings in both arms.

Table 14: Recording time points to be considered in an analysis with the same number of recordings

Treatment arms	**Recording time points (weeks)[a]**																	
Selinexor + bortezomib + dexamethasone	0		5			10		15		20			25		30		35	…
Bortezomib + dexamethasone	0			6	9			15			21	24		29		34		…
a. The recordings at weeks 3, 12 and 18 in the comparator arm with bortezomib + dexamethasone are not included.																		

Regardless of the question of the different number of recording time points, it is clear from looking at the graphs on the PROs that a model with linear adjustment, which is done in a random coefficients model, is not appropriate.

I 4.2 Risk of bias

Table 15 describes the risk of bias for the results of the relevant outcomes.

Table 15: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: selinexor + bortezomib + dexamethasone vs. bortezomib + dexamethasone

Study	Study level	Outcomes										
		Overall survival	Symptoms (EORTC QLQ-C30 and EORTC QLQ-CIPN20)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Gastrointestinal disorders (SOC, severe AEs[a])	Peripheral neuropathy (PT, severe AEs[a])	Cataract (PT, severe AEs[a])	Further specific AEs[a, b]
BOSTON	L	H[c]	–[d]	–[d]	–[d]	H[e, f]	H[e, f]	H[e, g]	H[e, f]	H[e, f]	H[e, f]	H[e, h]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. The following events are considered (coded according to MedDRA): "cardiac disorders" (SOC, AEs), "respiratory, thoracic and mediastinal disorders" (SOC, SAEs), "blood and lymphatic system disorders" (SOC, severe AES), "infections and infestations" (SOC, severe AEs), "general disorders and administration site conditions" (SOC, severe AEs) and "metabolism and nutrition disorders" (SOC, severe AEs).
c. High proportion of patients who switched from the comparator arm to the intervention arm during the course of the study (38.6%); no information on the time points of switching; no information on subsequent therapies.
d. No suitable data available; for the reasoning, see Section I 4.1.
e. Analysis by safety population: all patients who were included in the study and received at least one dose of the study medication, analysis by the treatment the patient received (SVd or Vd).
f. Patients with incomplete observation due to clearly different reasons for treatment discontinuation.
g. Lack of blinding in the presence of subjective decision on treatment discontinuation.
h. Lack of blinding in specific AEs that are non-severe or non-serious.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer-Core 30; EORTC QLQ-CIPN20: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Chemotherapy-Induced Peripheral Neuropathy 20; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

For the results on overall survival, the risk of bias is rated as high, since due to the lack of information on the subsequent therapies used, it cannot be assessed whether the patients in both treatment arms received guideline-compliant subsequent antineoplastic therapies. In addition, approximately 39% of patients in the comparator arm crossed over to treatment with selinexor + bortezomib + dexamethasone (n = 66 [32%]) or selinexor + dexamethasone (14 [7%]) in the sense of treatment switching [23]. There is no information available regarding the times at which the patients switched treatment or reasons for the switch. The sensitivity analyses presented by the company using a rank preserving structural failure time model (RPSFTM) are not usable for the benefit assessment. Firstly, this complex analysis lacks adequate, detailed documentation [23] to assess the analysis performed. In particular, the underlying assumption of the common treatment effect is to be viewed critically, especially in the oncological field. Secondly, the accelerated failure time factor Ψ, which is estimated in the RPSFTM, is not an

effect measure for a difference between treatments for overall survival. Instead, Ψ can be used to describe for a patient in the intervention arm the scaling factor by which the survival time changes compared with the time the patient would have experienced under the control intervention. Ψ could be used to calculate survival time analyses and estimate hazard ratios, but the company did not present these analyses. Treatment switching is also taken into account in the high risk of bias for this outcome.

No suitable data are available for the outcomes of symptoms (EORTC QLQ-C30, EORTC QLQ-CIPN20), health status (EQ-5D VAS), or health-related quality of life (EORTC QLQ-C30) (see Section I 4.1).

The risk of bias of the results on the outcomes of SAEs, severe AEs, as well as gastrointestinal disorders (severe AEs), peripheral neuropathy (severe AEs), cataract (severe AEs), and further specific AEs is rated as high. Even though the median treatment durations are comparable between the treatment arms, there are clear differences in the reasons for treatment discontinuation. At the data cut-off on 15 February 2021, 83 (43%) patients in the intervention arm had discontinued treatment prematurely due to disease progression, compared with 123 (60%) in the comparator arm. In contrast, 89 (46%) patients in the intervention arm discontinued treatment for other reasons (discontinuation by the patient, AE/toxicity, lost to follow-up, noncompliance, physician's decision, other), compared with 60 (29%) patients in the comparator arm. For the mentioned outcomes of the category of side effects, there are incomplete observations for various reasons due to the follow-up observation linked to the treatment duration and a possible association between outcome and reason for treatment discontinuation.

The risk of bias of the results for the outcome of discontinuation due to AEs as well as for the specific AEs that are non-severe/non-serious is additionally rated as high due to the lack of blinding.

Summary assessment of the certainty of conclusions

The open-label RCT BOSTON is available for the assessment. The risk of bias is rated as high for the results of overall survival and side effects.

As described in Section I 3.2, the use of bortezomib beyond 8 cycles is not in compliance with the specifications in the SPC of bortezomib [15]. Furthermore, it ultimately remains unclear from the information provided by the company whether autologous stem cell therapy was not suitable for the patients at the time of the current therapy. Due to the small proportion of patients pretreated with autologous stem cell therapy, the certainty of conclusions of the results is additionally reduced.

In this situation, only hints, e.g. of an added benefit, can therefore be derived on the basis of the BOSTON study.

I 4.3 Results

Table 16 summarizes the results of the comparison of selinexor + bortezomib + dexamethasone with bortezomib + dexamethasone for adult patients with multiple myeloma who have received at least one prior therapy. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. The Kaplan-Meier curves on the included outcomes are presented in I Appendix B of the full dossier assessment, whereas the results on common AEs, SAEs, severe AEs, and discontinuations due to AEs are found in I Appendix C of the full dossier assessment.

Table 16: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: selinexor + bortezomib + dexamethasone vs. bortezomib + dexamethasone (multipage table)

Study **Outcome category** **Outcome**	**Selinexor + bortezomib + dexamethasone**		**Bortezomib + dexamethasone**		**Selinexor + bortezomib + dexamethasone vs. bortezomib + 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]**
Study BOSTON					
Mortality (data cut-off 22 March 2022)					
Overall survival	195	36.7 [31.7; NC] 74 (38.0)	207	NA [26.9; NC] 83 (40.1)	0.93 [0.67; 1.27]; 0.633
Morbidity (data cut-off 15 February 2021)					
Symptoms (EORTC QLQ-C30)				No suitable data[b]	
EORTC-QLQ-CIPN20				No suitable data[b]	
Health status (EQ-5D VAS)				No suitable data[b]	
Health-related quality of life (data cut-off 15 February 2021)					
EORTC QLQ-C30				No suitable data[b]	
Side effects (data cut-off 5 June 2022)					
AEs (supplementary information)	195	– 194 (99.5)	204	– 198 (97.1)	–
SAEs	195	– 109 (55.9)	204	– 79 (38.7)	RR: 1.44 [1.17; 1.79]; < 0.001[c]
Severe AEs[d]	195	– 169 (86.7)	204	– 128 (62.7)	RR: 1.38 [1.23; 1.56]; < 0.001[c]
Discontinuation due to AEs	195	– 42 (21.5)	204	– 35 (17.2)	RR: 1.26 [0.84; 1.88]; 0.275[c]
Gastrointestinal disorders (SOC, severe AEs[d])	195	– 35 (17.9)	204	– 7 (3.4)	RR: 5.23 [2.38; 11.50]; < 0.001[c]

Table 16: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: selinexor + bortezomib + dexamethasone vs. bortezomib + dexamethasone (multipage table)

Study Outcome category Outcome	Selinexor + bortezomib + dexamethasone		Bortezomib + dexamethasone		Selinexor + bortezomib + dexamethasone vs. bortezomib + 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]
Peripheral neuropathy (PT, severe AEs[d])	No suitable data[e]				
Cataract (PT, severe AEs[d])	195	– 22 (11.3)	204	– 4 (2.0)	RR: 5.75 [2.02; 16.40]; < 0.001[c]
Cardiac disorders (SOC, AEs)	195	– 35 (17.9)	204	– 16 (7.8)	RR: 2.29 [1.31; 4.00]; 0.003[c]
Respiratory, thoracic and mediastinal disorders (SOC, SAEs)	195	– 14 (7.2)	204	– 5 (2.5)	RR: 2.93 [1.08; 7.98]; 0.027[c]
Blood and lymphatic system disorders (SOC, severe AEs[d])	195	– 96 (49.2)	204	– 48 (23.5)	RR: 2.09 [1.57; 2.78]; < 0.001[c]
Infections and infestations (SOC, severe AEs[d])	195	– 65 (33.3)	204	– 36 (17.6)	RR: 1.89 [1.32; 2.70]; < 0.001[c]
General disorders and administration site conditions (SOC, severe AEs[d])	195	– 50 (25.6)	204	– 16 (7.8)	RR: 3.27 [1.93; 5.54]; < 0.001[c]
Metabolism and nutrition disorders (SOC, severe AEs[d])	195	– 43 (22.1)	204	– 17 (8.3)	RR: 2.65 [1.56; 4.48]; < 0.001[c]

a. HR [95% CI] (stratified Cox regression) and 2-sided p-value (stratified log-rank test); strata for regression and significance test: prior PI therapy (yes; no); number of anti-myeloma therapies (1; > 1); R-ISS stage at baseline (R-ISS stage III; R-ISS stage I/II; if R-ISS stage was not available, ISS stage was used).
b. See Section I 4.1 for more detailed reasoning.
c. Institute's calculation, effect estimate and 95% CI asymptotic; p-value unconditional exact test, (CSZ method according to [24]).
d. Operationalized as CTCAE grade ≥ 3.
e. At the final efficacy data cut-off on 15 February 2021, event rates for the PT peripheral neuropathy (severe AEs) were 9 (4.6) vs. 18 (8.8). At the later data cut-off on 5 June 2022, the event rates were 6 (3.1) and 13 (6.4). The lower number of events at the data cut-off on 5 June 2022 is not comprehensible. For this reason, the results for this AE are considered not interpretable.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer-Core 30; EORTC QLQ-CIPN20: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Chemotherapy-Induced Peripheral Neuropathy 20; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes (see Section I 4.2).

Mortality

Overall survival

For the outcome of overall survival, no statistically significant difference between treatment groups was found. However, there was an effect modification by the characteristic of age (see Section I 4.4). In the overall consideration of the present data, a meaningful interpretation of the results on overall survival is not possible. This results in no hint of an added benefit of selinexor + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone; an added benefit is therefore not proven.

Morbidity

Symptoms (EORTC QLQ-C30 and EORTC QLQ-CIPN20)

No suitable data are available for the outcomes on symptoms, recorded with the EORTC QLQ-C30 and the EORTC QLQ-CIPN20. This results in no hint of an added benefit of selinexor + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

No suitable data are available for the outcome of health status, recorded with the EQ-5D VAS. This results in no hint of an added benefit of selinexor + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

No suitable data are available for the outcome of health-related quality of life, recorded with the EORTC QLQ-C30 functional scales. This results in no hint of an added benefit of selinexor + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone; an added benefit is therefore not proven.

Side effects

SAEs and severe AEs

For the outcomes of SAEs and severe AEs, a statistically significant difference was found to the disadvantage of selinexor + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone. This results in a hint of greater harm of selinexor + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone for each of these outcomes.

Discontinuation due to AEs

No statistically significant difference was found between treatment groups for the outcome of discontinuation due to AEs. This results in no hint of an added benefit of selinexor +

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

Gastrointestinal disorders (severe AEs) and cataract (severe AEs)

For each of the outcomes of gastrointestinal disorders (severe AEs) and cataract (severe AEs), a statistically significant difference was found to the disadvantage of selinexor + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone. This results in a hint of greater harm of selinexor + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone for each of these outcomes.

Peripheral neuropathy (severe AEs)

No suitable data are available for the outcome of peripheral neuropathy (severe AEs). This results in no hint of greater or lesser harm from selinexor + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone; greater or lesser harm is therefore not proven.

Further specific AEs

Cardiac disorders (AEs), respiratory, thoracic and mediastinal disorders (SAEs), blood and lymphatic system disorders (severe AEs), infections and infestations (severe AEs), general disorders and administration site conditions (severe AEs), metabolism and nutrition disorders (severe AEs)

A statistically significant difference to the disadvantage of selinexor + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone was shown for each of the outcomes of cardiac disorders (AEs), respiratory, thoracic and mediastinal disorders (SAEs), blood and lymphatic system disorders (severe AEs), general disorders and administration site conditions (severe AEs) and metabolism and nutrition disorders (severe AEs). This results in a hint of greater harm of selinexor + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone for each of these outcomes.

For the outcome of infections and infestations (severe AEs), there is an effect modification by the characteristic of sex (see Section I 4.4). For women, there is a hint of greater harm of selinexor + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone. For men, there is no hint of greater or lesser harm of selinexor + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone; greater or lesser harm is therefore not proven for male patients.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics were considered to be relevant for the present benefit assessment:

- sex (men/women)
- age (< 65/≥ 65 years)
- R-ISS stage (stage I and stage II/stage III)

The mentioned characteristics were defined a priori.

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

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

Table 17 summarizes the subgroup results of the comparison of selinexor + bortezomib + dexamethasone with bortezomib + dexamethasone for adult patients with multiple myeloma who have received at least one prior therapy.

Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Kaplan-Meier curves on the presented event time analyses can be found in I Appendix B.2 of the full dossier assessment.

Table 17: Subgroups (overall survival, morbidity, health-related quality of life, side effects) – RCT, direct comparison: selinexor + bortezomib + dexamethasone vs. bortezomib + dexamethasone

Study Outcome Characteristic Subgroup	Selinexor + bortezomib + dexamethasone N	Median time to event in months [95% CI] Patients with event n (%)	Bortezomib + dexamethasone N	Median time to event in months [95% CI] Patients with event n (%)	Selinexor + bortezomib + dexamethasone vs. bortezomib + dexamethasone HR [95% CI]	p-value
Study BOSTON						
Mortality						
Overall survival[a]						
Age						
< 65 years	86	34.2 [24.6; NC] 38 (44.2)	75	NA 21 (28.0)	1.85 [1.05; 3.27]	0.031
≥ 65 years	109	NA [32.2; NC] 36 (33.0)	132	26.6 [21.4; NC] 62 (47.0)	0.63 [0.41; 0.95]	0.028
Total					Interaction:	0.003
Side effects						
Infections and infestations (SOC, severe AEs[b])[c]						
Sex						
Men	115	– 29 (25.2)	113	– 22 (19.5)	RR: 1.30 [0.79; 2.11][d]	0.321
Women	80	– 36 (45.0)	91	– 14 (15.4)	RR: 2.93 [1.71; 5.02][d]	< 0.001
Total					Interaction:	0.028

a. Data cut-off 22 March 2022.
b. Operationalized as CTCAE grade ≥ 3.
c. Data cut-off 5 June 2022.
d. Institute's calculation, effect estimate and 95% CI asymptotic; p-value unconditional exact test, (CSZ method according to [24]).

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer-Core 30; EORTC QLQ-CIPN20: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Chemotherapy-Induced Peripheral Neuropathy 20; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; RR: relative risk; SOC: System Organ Class

Mortality

Overall survival

For the outcome of overall survival, there was an effect modification by the characteristic of age. A statistically significant difference in favour of selinexor + bortezomib + dexamethasone in comparison with the ACT was shown for patients ≥ 65 years of age at study inclusion.

A statistically significant effect to the disadvantage of selinexor + bortezomib + dexamethasone in comparison with the ACT was shown for patients < 65 years of age.

No statistically significant difference between treatment groups was shown on the basis of the results of the total population. However, as described above, this result has a high risk of bias already due to the high proportion of patients with treatment switching from the comparator arm to the intervention arm and the missing data on subsequent therapies. Furthermore, there are uncertainties regarding the transferability of the results to the German health care context. In addition, there is a late crossing of the Kaplan-Meier curves for the total population. The observed effect modification by the characteristic of age might explain the crossing graphs. Without further information on the number of patients in the respective subgroup (age ≥ 65 years and age < 65 years) who switched from the comparator arm to treatment with selinexor and on the time points the treatment switches took place, the results on overall survival cannot be meaningfully interpreted.

In the overall assessment, the results for the outcome of overall survival are not considered to be meaningfully interpretable and are not used for deriving the added benefit. This results in no hint of an added benefit of selinexor + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone; an added benefit is therefore not proven.

Side effects

Further specific AEs

Infections and infestations (severe AEs)

For the outcome of infections and infestations (severe AEs), there was an effect modification by the characteristic of sex. A statistically significant effect to the disadvantage of selinexor + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone was shown for women. This results in a hint of greater harm of selinexor + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone for women.

For men, in contrast, there was no statistically significant difference between the treatment groups. This results in no hint of greater or lesser harm from selinexor + bortezomib + dexamethasone in comparison with the ACT; greater or lesser harm is therefore not proven for men.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *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.

I 5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section I 4 (see Table 18).

Table 18: Extent of added benefit at outcome level: selinexor + bortezomib + dexamethasone vs. bortezomib + dexamethasone (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Selinexor + bortezomib + dexamethasone vs. bortezomib + dexamethasone** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	Not meaningfully interpretable	Lesser/added benefit not proven
Morbidity		
Symptoms (EORTC QLQ-C30)	No suitable data available	Lesser/added benefit not proven
Symptoms (EORTC QLQ-CIPN20)	No suitable data available	Lesser/added benefit not proven
Health status (EQ-5D VAS)	No suitable data available	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30	No suitable data available	Lesser/added benefit not proven

Table 18: Extent of added benefit at outcome level: selinexor + bortezomib + dexamethasone vs. bortezomib + dexamethasone (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Selinexor + bortezomib + dexamethasone vs. bortezomib + dexamethasone** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
SAEs	55.9 vs. 38.7 RR: 1.44 [1.17; 1.79] RR: 0.69 [0.56; 0.85][c] p < 0.001 Probability: "hint"	Outcome category: serious/severe side effects $0.75 < CI_u < 0.90$ Greater harm, extent: "considerable"
Severe AEs	86.7 vs. 62.7 RR: 1.38 [1.23; 1.56] RR: 0.72 [0.64; 0.81][c] p < 0.001 Probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Greater harm, extent: "considerable"
Discontinuation due to AEs	21.5 vs. 17.2 RR: 1.26 [0.84; 1.88] RR: 0.79 [0.53; 1.19][c] p = 0.275	Greater/lesser harm not proven
Gastrointestinal disorders (severe AEs)	17.9 vs. 3.4 RR: 5.23 [2.38; 11.50] RR: 0.19 [0.09; 0.42][c] p < 0.001 Probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm, extent: "major"
Peripheral neuropathy (severe AEs)	No suitable data	Greater/lesser harm not proven
Cataract (severe AEs)	11.3 vs. 2.0 RR: 5.75 [2.02; 16.40] RR: 0.17 [0.06; 0.50][c] p < 0.001 Probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm, extent: "major"
Cardiac disorders (SOC, AEs)	17.9 vs. 7.8 RR: 2.29 [1.31; 4.00] RR: 0.44 [0.25; 0.76][c] p = 0.003 Probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm, extent: "considerable"
Respiratory, thoracic and mediastinal disorders (SAEs)	7.2 vs. 2.5 RR: 2.93 [1.08; 7.98] RR: 0.34 [0.13; 0.93][c] p = 0.027 Probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Greater harm, extent: "minor"
Blood and lymphatic system disorders (severe AEs)	49.2 vs. 23.5 RR: 2.09 [1.57; 2.78] RR: 0.48 [0.36; 0.64][c] p < 0.001 Probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm, extent: "major"

Table 18: Extent of added benefit at outcome level: selinexor + bortezomib + dexamethasone vs. bortezomib + dexamethasone (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Selinexor + bortezomib + dexamethasone vs. bortezomib + dexamethasone** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Infections and infestations (severe AEs)	33.3 vs. 17.6 RR: 1.89 [1.32; 2.70] RR: 0.53 [0.37; 0.76][c] p < 0.001 Probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Greater harm, extent: "considerable"
Sex		
Men	25.2 vs. 19.5 RR: 1.30 [0.79; 2.11] p = 0.321	Greater/lesser harm not proven
Women	45.0 vs. 15.4 RR: 2.93 [1.71; 5.02] RR: 0.34 [0.20; 0.58][c] p < 0.001 Probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm, extent: "major"
General disorders and administration site conditions (severe AEs)	25.6 vs. 7.8 RR: 3.27 [1.93; 5.54] RR: 0.31 [0.18; 0.25][c] p < 0.001 Probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm, extent: "major"
Metabolism and nutrition disorders (severe AEs)	22.1 vs. 8.3 RR: 2.65 [1.56; 4.48] RR: 0.38 [0.22; 0.64][c] p < 0.001 Probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm, extent: "major"

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer-Core 30; EORTC QLQ-CIPN20: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Chemotherapy-Induced Peripheral Neuropathy 20; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale

I 5.2 Overall conclusion on added benefit

Table 19 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

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

Positive effects	**Negative effects**
Total observation period	
–	–
Shortened observation period	
–	Non-serious/non-severe side effects ▪ Cardiac disorders: hint of greater harm – extent: "considerable" Serious/severe side effects ▪ SAEs: hint of greater harm – extent: "considerable" including ▫ respiratory, thoracic and mediastinal disorders: hint of greater harm – extent: "minor" ▪ Severe AEs: hint of greater harm – extent: "considerable" including ▫ gastrointestinal disorders: hint of greater harm – extent: "major" ▫ cataract: hint of greater harm – extent: "major" ▫ blood and lymphatic system disorders: hint of greater harm – extent: "major" ▫ infections and infestations - sex (women): hint of greater harm – extent: "major" ▫ general disorders and administration site conditions: hint of greater harm – extent: "major" ▫ metabolism and nutrition disorders: hint of greater harm – extent: "major"
The results on the outcome of overall survival are not meaningfully interpretable.	
No suitable data are available for the patient-reported outcomes on morbidity and health-related quality of life.	
AE: adverse event; SAE: serious adverse event	

Overall, this results in exclusively negative effects of selinexor + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone. All these negative effects are related to outcomes in the category of side effects and only refer to the shortened time period until 30 days after discontinuation of treatment.

Since no suitable data are available for the outcome categories of morbidity and health-related quality of life, and the results for the outcome of mortality cannot be meaningfully interpreted, it is not possible to weigh up the benefits and harms.

A meaningful interpretation of the results on overall survival is not possible in the present data situation. This also concerns the observed effect modification by age, which shows a disadvantage for patients < 65 years and an advantage for those ≥ 65 years of age. Neither added benefit nor lesser benefit can be derived on the basis of the data situation described.

In summary, added benefit of selinexor + bortezomib + dexamethasone in comparison with the ACT is not proven for adult patients with multiple myeloma who have received at least one prior therapy.

Table 20 summarizes the result of the assessment of the added benefit of selinexor + bortezomib + dexamethasone in comparison with the ACT.

Table 20: Selinexor + bortezomib + dexamethasone – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with multiple myeloma who have received at least one previous treatment[b, c]	▪ Bortezomib in combination with pegylated liposomal doxorubicin or ▪ **bortezomib in combination with dexamethasone** or ▪ lenalidomide 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	Added benefit not proven
a. Presented is the 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 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. c. It is assumed that the special situation of refractory patients is taken into account when choosing the ACT. 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 the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

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

1. Institute for Quality and Efficiency in Health Care. General Methods; Version 6.1 [online]. 2022 [Accessed: 17.08.2022]. URL: https://www.iqwig.de/methoden/general-methods_version-6-1.pdf.

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

3. Karyopharm Therapeutics. A Phase 3 randomized, controlled, open-label study of Selinexor, Bortezomib, and Dexamethasone (SVd) versus Bortezomib and Dexamethasone (Vd) in patients with relapsed or refractory multiple myeloma (RRMM); Clinical Study Report KCP-330-023 [unpublished]. 2021.

4. Karyopharm Therapeutics. Bortezomib, Selinexor, and Dexamethasone in Patients With Multiple Myeloma [online]. 2021 [Accessed: 19.10.2022]. URL: https://ClinicalTrials.gov/show/NCT03110562.

5. Karyopharm Therapeutics. A Phase 3 Randomized, Controlled, Open-label Study of Selinexor, Bortezomib, and Dexamethasone (SVd) versus Bortezomib and Dexamethasone (Vd) in Patients with Relapsed or Refractory Multiple Myeloma [online]. 2017 [Accessed: 19.10.2022]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-003957-14.

6. Karyopharm Therapeutics. A Phase 3 Randomized, Controlled, Open-LabelStudy Of Selinexor, Bortezomib, AND Dexamethasone (SVD) Versus Bortezomib AND Dexamethasone (VD) In Patients With Relapsed Or Refractory Multiple Myeloma (RRMM) - BOSTON [online]. 2021 [Accessed: 19.10.2022]. URL: http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=19811.

7. Grosicki S, Simonova M, Spicka I et al. Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomised, open-label, phase 3 trial. Lancet 2020; 396(10262): 1563-1573. https://dx.doi.org/10.1016/S0140-6736(20)32292-3.

8. Auner HW, Gavriatopoulou M, Delimpasi S et al. Effect of age and frailty on the efficacy and tolerability of once-weekly selinexor, bortezomib, and dexamethasone in previously treated multiple myeloma. Am J Hematol 2021. https://dx.doi.org/10.1002/ajh.26172.

9. Mateos MV, Gavriatopoulou M, Facon T et al. Effect of prior treatments on selinexor, bortezomib, and dexamethasone in previously treated multiple myeloma. J Hematol Oncol 2021; 14(1): 1-5.

10. Richard S, Chari A, Delimpasi S et al. Selinexor, bortezomib, and dexamethasone versus bortezomib and dexamethasone in previously treated multiple myeloma: Outcomes by cytogenetic risk. Am J Hematol 2021; 96(9): 1120-1130. https://dx.doi.org/10.1002/ajh.26261.

11. Delimpasi S, Mateos MV, Auner HW et al. Efficacy and tolerability of once-weekly selinexor, bortezomib, and dexamethasone in comparison with standard twice-weekly bortezomib and dexamethasone in previously treated multiple myeloma with renal impairment: Subgroup analysis from the BOSTON study. Am J Hematol 2022; 97(3): E83-E86. https://dx.doi.org/10.1002/ajh.26434.

12. Dolph M, Tremblay G, Gilligan AM et al. Network Meta-Analysis of Once Weekly Selinexor-Bortezomib-Dexamethasone in Previously Treated Multiple Myeloma. JHEOR 2021; 8(2): 26-35. https://dx.doi.org/10.36469/001c.27080.

13. Dolph M, Tremblay G, Leong H. Cost Effectiveness of Triplet Selinexor-Bortezomib-Dexamethasone (XVd) in Previously Treated Multiple Myeloma (MM) Based on Results from the Phase III BOSTON Trial. Pharmacoeconomics 2021; 39(11): 1309-1325. https://dx.doi.org/10.1007/s40273-021-01068-9.

14. European Medicines Agency. Nexpovio; Assessment report [online]. 2022 [Accessed: 25.11.2022]. URL: https://www.ema.europa.eu/documents/variation-report/nexpovio-h-c-005127-ii-0001-g-epar-assessment-report_en.pdf.

15. Medac. Bortezomib medac 3,5 mg Pulver zur Herstellung einer Injektionslösung [online]. 2021 [Accessed: 25.11.2022]. URL: https://www.fachinfo.de/suche/fi/022999.

16. Takeda Pharmaceuticals America. Velcade full prescribing information [online]. 2021 [Accessed: 28.11.2022]. URL: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021602s046lbl.pdf.

17. Stemline. NEXPOVIO 20 mg Filmtabletten [online]. 2022 [Accessed: 01.12.2022]. URL: https://www.fachinfo.de/suche/fi/023843.

18. Jordan K, Jahn F, Feyer P et al. Antiemese bei medikamentöser Tumortherapie [online]. 2021 [Accessed: 13.12.2022]. URL: https://www.onkopedia.com/de/onkopedia/guidelines/antiemese-bei-medikamentoeser-tumortherapie/@@guideline/html/index.html.

19. Leitlinienprogramm Onkologie. S3-Leitlinie Diagnostik, Therapie und Nachsorge für Patienten mit monoklonaler Gammopathie unklarer Signifikanz (MGUS) oder Multiplem Myelom [online]. 2022 [Accessed: 25.11.2022]. URL: https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Multiples_Myelom/LL_Multiples_Myelom_Langversion_1.0.pdf.

20. Gemeinsamer Bundesausschuss. Mündliche Anhörung gemäß § 35 a Abs. 3 Satz 2 SGB V des Gemeinsamen Bundesausschusses; hier: Daratumumab (D-812) [online]. 2022 [Accessed: 01.12.2022]. URL: https://www.g-ba.de/downloads/91-1031-809/2022-08-08_Wortprotokoll_Daratumumab_D-812.pdf.

21. Wörmann B, Driessen C, Einsele H et al. Multiples Myelom [online]. 2018 [Accessed: 25.11.2022]. URL: https://www.onkopedia.com/de/onkopedia/guidelines/multiples-myelom/@@guideline/html/index.html.

22. Gemeinsamer Bundesausschuss. Antworten auf häufig gestellte Fragen zum Verfahren der Nutzenbewertung; Wie soll, vor dem Hintergrund der Veröffentlichung des Methodenpapiers 6.0 des IQWiG am 5. November 2020, derzeit in der Dossiererstellung mit der Bestimmung von klinischen Relevanzschwellen bei komplexen Skalen umgegangen werden? [online]. [Accessed: 05.08.2021]. URL: https://www.g-ba.de/themen/arzneimittel/arzneimittel-richtlinie-anlagen/nutzenbewertung-35a/faqs.

23. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Treatment Switching in onkologischen Studien; Arbeitspapier [online]. 2018 [Accessed: 10.12.2018]. URL: https://www.iqwig.de/download/GA14-04_Treatment-Switching-in-onkologischen-Studien_Arbeitspapier_V1-0.pdf.

24. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574. https://dx.doi.org/10.1016/0167-9473(94)90148-1.

The full report (German version) is published under https://www.iqwig.de/en/projects/a22-100.html.