IQWiG Reports – Commission No. A19-50

Pomalidomide (multiple myeloma) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Pomalidomid (multiples Myelom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 12 September 2019). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
DGHO	Deutschen Gesellschaft für Hämatologie und Medizinische Onkologie (German Society of Haematology and Oncology)
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
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)
ISS	International Staging System
PFS	progression-free survival
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-MY20	Quality of Life Questionnaire-Multiple Myeloma Module 20
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMQ	Standardized Medical Dictionary for Regulatory Activities Query
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug pomalidomide. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 11 June 2019.

Research question

The aim of the present report is the assessment of the added benefit of pomalidomide in combination with bortezomib and dexamethasone (pomalidomide + bortezomib + dexamethasone) in comparison with the appropriate comparator therapy (ACT) in adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide.

Table 2: Research question of the benefit assessment of pomalidomide

Therapeutic indication	**ACT[a]**
Adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide	▪ 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: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company chose bortezomib in combination with dexamethasone (bortezomib + dexamethasone) as comparator therapy and thus followed the G-BA's specification of the ACT.

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

Results

Study pool and study characteristics

Study MM-007 was included in the present benefit assessment.

The MM-007 study is an open-label, randomized, active controlled study on the comparison of pomalidomide + bortezomib + dexamethasone versus bortezomib + dexamethasone.

It enrolled adult patients (≥ 18 years) with multiple myeloma after 1 to 3 prior therapies, including lenalidomide for ≥ 2 consecutive cycles, with disease progression during or after their last pretreatment. In addition, the patients had to have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0, 1 or 2. Although prior stem cell transplantation or unsuitability for stem cell transplantation (according to the Summary of Product Characteristics (SPC) a precondition for bortezomib) was not an inclusion criterion, it is assumed on the basis of the treatment algorithm in the guidelines that stem cell transplantation was not indicated for patients without stem cell transplantation at the time point of study inclusion.

The patients were randomly assigned to the 2 treatment arms in a ratio of 1:1: 281 patients to the pomalidomide + bortezomib + dexamethasone arm and 278 patients to the bortezomib + dexamethasone arm.

The study treatment largely corresponded to the specifications of the respective SPC for pomalidomide, bortezomib and dexamethasone. The most important deviation was in the bortezomib + dexamethasone arm, as treatment with bortezomib was not discontinued after the maximum number of 8 cycles recommended in the SPC for bortezomib. In addition, patients > 75 years of age in the bortezomib + dexamethasone arm received 10 mg/day of dexamethasone and not the 20 mg/day recommended in the SPC of bortezomib.

Treatment with the randomized study medication was discontinued, among other things, when disease progression or unacceptable toxicity occurred. Subsequent anti-myeloma treatments were only allowed after the onset of progression. Switching from the control arm to the intervention arm was not a planned study intervention.

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).

Analyses on 2 data cut-offs are available. The first data cut-off was prespecified for PFS on reaching 320 events (progression or death) and was conducted on 26 October 2017. The second data cut-off was not prespecified and was conducted on 15 September 2018 for overall survival

at the request of the European Medicines Agency (EMA) in the framework of the extension of approval for pomalidomide.

The company presented analyses on all patient-relevant outcomes for the first data cut-off, whereas it only presented analyses on overall survival and side effects for the second data cut-off. The results of the second data cut-off were used for overall survival and side effects, and the results of the first data cut-off were used for morbidity and health-related quality of life.

Uncertainties of study MM-007

Number of bortezomib cycles

According to the SPC of bortezomib, pretreated patients can receive a total of 8 treatment cycles with bortezomib + dexamethasone. In the control arm of the MM-007 study, treatment with bortezomib + dexamethasone was more than 8 cycles in 39.6% of the patients. However, the company did not provide any information on how such prolonged administration of bortezomib affects the effects in comparison with the ACT.

On the basis of the information in the dossier, the influence of bortezomib administration for more than 8 cycles is ultimately unclear. The guidelines of the German Society of Haematology and Oncology (DGHO) do not provide any information on the duration of bortezomib therapy; it is recommended to treat patients up to 2 cycles after the best response.

Nevertheless, it is assumed that the possibility to administer bortezomib for more than 8 cycles does not question the relevance of the study. This uncertainty was taken into account in the derivation of the added benefit, however, and led to a limitation in the certainty of conclusions.

Reduced dexamethasone dose in patients > 75 years

In the MM-007 study, patients aged > 75 years received dexamethasone at a dose of 10 mg/day instead of 20 mg/day. This dose is in line with the SPC for pomalidomide, but cannot be inferred from the SPC for bortezomib.

The reduced dose of dexamethasone affected 16.4% of the patients in the bortezomib + dexamethasone arm. The available results do not allow to estimate the effect of the deviation from the recommended dexamethasone dose on the overall result of the dossier assessment. However, it is assumed that the reduced dose of dexamethasone reduces the interpretability of the study, but does not completely question it.

Risk of bias and certainty of conclusions of the results

The risk of bias across outcomes was rated as low for the MM-007 study; the outcome-specific risk of bias for the results of all outcomes except overall survival was rated as high.

On the one hand, this was due to the lack of blinding, on the other, to the differences in observation periods between the study arms. In addition, there were incomplete observations for potentially informative reasons for some outcomes. For the outcome “discontinuation due

to AEs" (≥ 1 drug component), there is also restricted certainty of results due to potentially competing events.

The certainty of conclusions of the study is also reduced because of the described uncertainty due to the use of bortezomib and the reduced dexamethasone dose in the comparator arm. As a result, at most hints, e.g. of an added benefit, can be derived on the basis of the MM-007 study. The outcome-specific assessment can deviate from this.

Results

Mortality – overall survival

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

Morbidity – symptoms (EORTC QLQ-C30 and QOL-MY20 symptom scales)

Symptom outcomes were recorded with the symptom scales of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and Quality of Life Questionnaire-Multiple Myeloma Module 20 (QLQ-MY20). The time to first deterioration by ≥ 10 points was considered in each case.

A statistically significant difference to the disadvantage of pomalidomide + bortezomib + dexamethasone was shown for the outcome "constipation". For an outcome of the category of non-serious/non-severe symptoms/late complications, the difference was no more than marginal, however. This resulted in no hint of lesser benefit or added benefit of pomalidomide + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone; lesser benefit or added benefit is therefore not proven.

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

Health-related quality of life – EORTC QLQ-C30 and QLQ-MY20 functional scales

Outcomes of health-related quality of life were recorded with the functional scales of the EORTC QLQ-C30 and QLQ-MY20. The time to first deterioration by ≥ 10 points was considered in each case.

No statistically significant differences between the treatment arms were shown for the outcomes "physical functioning", "role functioning", "cognitive functioning", "emotional functioning", "future perspective" and "body image". In each case, this resulted in no hint of an added benefit

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

No statistically significant difference between the treatment arms was shown for each of the outcomes “global health status” and “social functioning”.

An effect modification by the characteristic International Staging System (ISS) stage was shown for the outcome “global health status”, however. Hence, for patients with ISS stage I or II, there was no hint of an added benefit of pomalidomide + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone; an added benefit is therefore not proven. For patients with ISS stage III, in contrast, there was a hint of an added benefit of pomalidomide + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone.

There was an effect modification by the characteristic “number of prior anti-myeloma regimens” for the outcome “social functioning”. For patients with > 1 regimen, there was no hint of an added benefit of pomalidomide + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone; an added benefit is therefore not proven. For patients with 1 regimen, in contrast, there was a hint of greater harm of pomalidomide + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone.

Side effects

A statistically significant difference to the disadvantage of pomalidomide + bortezomib + dexamethasone was shown for the outcomes “serious adverse events (SAEs)” and “severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)”. This resulted in a hint of greater harm of pomalidomide + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone in each case.

There was no statistically significant difference between the treatment arms for the outcome “discontinuation due to AEs (≥ 1 drug component)”. This resulted in no hint of greater or lesser harm from pomalidomide + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone; greater or lesser harm is therefore not proven.

Specific adverse events

There was no statistically significant difference between the treatment arms for the outcome “peripheral neuropathy (Standardized Medical Dictionary for Regulatory Activities Query [SMQ], AE)”. This resulted in no hint of greater or lesser harm from pomalidomide + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone; greater or lesser harm is therefore not proven.

A statistically significant difference to the disadvantage of pomalidomide + bortezomib + dexamethasone was shown for the outcome “venous thromboembolic event (SMQ, AE)”. This resulted in a hint of greater harm of pomalidomide + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone.

A statistically significant difference to the disadvantage of pomalidomide + bortezomib + dexamethasone was shown for the outcome "neutropenia (PT, severe AEs [CTCAE grade ≥ 3])". There was a high certainty of conclusions despite the high risk of bias because an effect in the present magnitude cannot be explained by different observation periods in the treatment arms alone. In addition, the effect occurred already early in the course of the study. Hence, an indication of greater harm from pomalidomide + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone was derived for this outcome.

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

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

In the overall consideration, based on the total population, there are only negative effects of pomalidomide + bortezomib + dexamethasone compared with bortezomib + dexamethasone with different probabilities (hints or indication) and different extents (minor to major) for several side effect outcomes that can be allocated to the outcome category of serious/severe side effects.

For the outcomes of health-related quality of life, a positive effect was shown for the subgroup of patients in ISS stage III (hint of considerable added benefit in the EORTC QLQ-C30 – functional scales, global health status), and a negative effect for the subgroup of patients with one prior anti-myeloma regimen (hint of lesser benefit of minor extent in the EORTC QLQ-C30 – functional scales, social functioning).

For the patients in ISS stage III, the negative effects from side effects outweighed the positive effect in global health status. Overall, this resulted in lesser benefit for the total population. Considering the certainty of conclusions of the superordinate outcomes of side effects (SAEs and severe AEs [CTCAE grade ≥ 3]), a hint of lesser benefit was derived.

In summary, there is a hint of lesser benefit of pomalidomide + bortezomib + dexamethasone versus bortezomib + dexamethasone for patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide.

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

[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: Pomalidomide – 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 prior treatment regimen including lenalidomide	▪ 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	Hint of lesser benefit
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

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

2.2 Research question

The aim of the present report is the assessment of the added benefit of pomalidomide in combination with bortezomib and dexamethasone (pomalidomide + bortezomib + dexamethasone) in comparison with the ACT in adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide.

This resulted in one research question for the present assessment, for which the G-BA specified the ACT presented in Table 4.

Table 4: Research question of the benefit assessment of pomalidomide

Therapeutic indication	**ACT[a]**
Adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide	▪ 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: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company chose bortezomib in combination with dexamethasone (bortezomib + dexamethasone) as comparator therapy and thus followed the G-BA's specification of the ACT.

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

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on pomalidomide (status: 2 April 2019)
- bibliographical literature search on pomalidomide (last search on 2 April 2019)
- search in trial registries for studies on pomalidomide (last search on 2 April 2019)

To check the completeness of the study pool:

- search in trial registries for studies on pomalidomide (last search on 18 June 2019)

The check identified no additional relevant study.

2.3.1 Studies included

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

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

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
MM-007	Yes	Yes	No
a: Study sponsored by the company. RCT: randomized controlled trial; vs.: versus			

Section 2.6 contains a reference list for the studies included.

2.3.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: pomalidomide + 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]
MM-007	RCT, open-label, parallel	Adult patients (≥ 18 years) with multiple myeloma with ▪ 1–3 prior therapies, including lenalidomide for ≥ 2 consecutive cycles ▪ disease progression during or after their last pretreatment ▪ ECOG PS ≤ 2	Pomalidomide + bortezomib + dexamethasone (N = 281) bortezomib + dexamethasone (N = 278)	Screening: ≤ 28 days before randomization Treatment: until death, disease progression, unacceptable toxicity, withdrawal of consent Observation[b, c]: outcome-specific, at most until end of study	133 centres in Canada, Europe, Israel, Japan, Russia, Turkey, USA 1/2013–ongoing First data cut-off: 26 Oct 2017 Second data cut-off: 15 Sep 2018	Primary: PFS 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 only include information on relevant available outcomes for this benefit assessment.
b: At least 5 years from randomization of the last study participant.
c: Outcome-specific information is provided in Table 9.

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

Table 7: Characteristics of the interventions – RCT, direct comparison: pomalidomide + bortezomib + dexamethasone vs. bortezomib + dexamethasone

Study	Intervention	Comparison
MM-007	Pomalidomide 4 mg orally on days 1 to 14 + bortezomib 1.3 mg/m² body surface area IV[a] or SC ▪ cycles 1–8: on days 1, 4, 8, 11 ▪ from cycle 9: on days 1, 8 + dexamethasone 20 mg (≤ 75 years) or 10 mg (> 75 years) orally ▪ cycles 1–8: on days 1, 2, 4, 5, 8, 9, 11, 12 ▪ from cycle 9: on days 1, 2, 8, 9 length of cycle: 21 days	 Bortezomib 1.3 mg/m² body surface area IV[a] or SC ▪ cycles 1–8: on days 1, 4, 8, 11 ▪ from cycle 9: on days 1, 8 + dexamethasone 20 mg (≤ 75 years) or 10 mg (> 75 years) orally ▪ cycles 1–8: on days 1, 2, 4, 5, 8, 9, 11, 12 ▪ from cycle 9: on days 1, 2, 8, 9 length of cycle: 21 days
	Treatment adjustments ▪ pomalidomide, bortezomib: dose reductions in compliance with the respective SPC as well as treatment interruption and discontinuation[b] allowed ▪ dexamethasone: dose reductions in compliance with the SPC of pomalidomide as well as treatment interruption and discontinuation allowed	
	Pretreatment **Required:** ▪ 1 to 3 prior myeloma therapies (including lenalidomide for ≥ 2 consecutive cycles)[c] **Not allowed:** ▪ 14 days before start of the study: plasmapheresis, major surgery (except kyphoplasty), radiotherapy[d], any systemic anti-myeloma therapy ▪ 3 weeks before the start of the study: ≥ 10 mg/day prednisone or equivalent steroid **Concomitant treatment** **Required:** ▪ thrombosis prophylaxis[e] with low-dose acetylsalicylic acid, low molecular weight heparin or equivalent medication **Allowed:** ▪ herpes zoster prophylaxis for all patients under bortezomib treatment, e.g. oral aciclovir or equivalent antiviral medication according to institutional guidelines ▪ for the treatment of complications from myeloma or myeloma treatment at the investigator's discretion: ▫ antibiotics, analgesics, antihistamines ▫ platelet, erythrocyte and fresh frozen plasma transfusions ▫ bisphosphonates and haematopoietic growth factors ▪ radiotherapy for pathological fractures or to treat bone pain ▪ inhaled, local, intranasal corticosteroids or local steroid injections ▪ only if medically required: QTc-time prolonging drugs **Not allowed:** ▪ other anti-myeloma therapies ▪ chronic steroid use (except study medication dexamethasone) and any immunosuppressants	

(continued)

Table 7: Characteristics of the interventions – RCT, direct comparison: pomalidomide + bortezomib + dexamethasone vs. bortezomib + dexamethasone (continued)

a: The study was started with bortezomib IV; this affected 15 vs. 20 patients. Due to the lower neurotoxicity of bortezomib when applied SC, treatment in both arms was switched to bortezomib SC in the course of the study.
b: In case of discontinuation of treatment with pomalidomide in the intervention arm or bortezomib in the comparator arm, the total study treatment had to be discontinued.
c: When using the 2-week dosage regimen in a dosage of 1.3 mg/m^2, prior bortezomib-containing therapy was only permitted if no progression of the disease had occurred during therapy or within 60 days of the last dose.
d: Except local treatment of myeloma-associated bone lesions.
e: Allowed in the pomalidomide arm in all patients, in the bortezomib arm in patients with a history of deep vein thrombosis or pulmonary embolism, in all other patients in the bortezomib arm at the discretion of the investigator.
IV: intravenous; QTc: frequency-corrected QT interval; RCT: randomized controlled trial; SC: subcutaneous; SPC: Summary of Product Characteristics; vs.: versus

Study characteristics

The MM-007 study is an open-label, randomized, active controlled study on the comparison of pomalidomide + bortezomib + dexamethasone versus bortezomib + dexamethasone. The ongoing study is conducted in 133 centres in Canada, Europe, Israel, Japan, Russia, Turkey and USA. Recruitment was from 7 January 2013 until 15 May 2017.

It enrolled adult patients (≥ 18 years) with multiple myeloma after 1 to 3 prior therapies, including lenalidomide for ≥ 2 consecutive cycles, with disease progression during or after their last pretreatment. In addition, the patients had to have an ECOG PS of 0, 1 or 2. Prior stem cell transplantation or unsuitability for stem cell transplantation was not an inclusion criterion. According to the SPC of bortezomib [3], however, prior stem cell transplantation or unsuitability for stem cell transplantation is a precondition for initiating treatment with bortezomib + dexamethasone. About 42% of the patients in the MM-007 study did not have prior stem cell transplantation. It is assumed on the basis of the treatment algorithm in the guidelines (e.g. [4,5]) that stem cell transplantation was not indicated for these patients.

The patients were stratified by age (≤ 75 versus > 75 years), number of prior anti-myeloma regimens (1 versus > 1) and beta-2 microglobulin level at screening (< 3.5 mg/L versus ≥ 3.5 to ≤ 5.5 mg/L versus > 5.5 mg/L) and randomly assigned to the 2 treatment arms in a ratio of 1:1: 281 patients to the pomalidomide + bortezomib + dexamethasone arm and 278 patients to the bortezomib + dexamethasone arm.

The study treatment (see Table 7) largely corresponded to the specifications of the respective SPCs for pomalidomide [6], bortezomib [3] and dexamethasone, e.g. [7]. The most important deviation was in the bortezomib + dexamethasone arm, as treatment with bortezomib was not discontinued after the maximum number of 8 cycles recommended in the SPC for bortezomib. In addition, patients > 75 years of age in the bortezomib + dexamethasone arm received 10 mg/day of dexamethasone and not the 20 mg/day recommended in the SPC of bortezomib (see below under uncertainties of the study).

Treatment with the randomized study medication was discontinued, among other things, when disease progression or unacceptable toxicity occurred. Subsequent anti-myeloma treatments were only allowed after the onset of progression. Switching from the control arm to the intervention arm (treatment switching in the sense of [8]) was not a planned study intervention.

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

Data cut-offs

Analyses on 2 data cut-offs are available. The first data cut-off was prespecified for PFS on reaching 320 events (progression or death) and was conducted on 26 October 2017. The second data cut-off was not prespecified and was conducted on 15 September 2018 for overall survival at the request of the EMA in the framework of the extension of approval for pomalidomide. The final analysis is planned after reaching 379 deaths; according to the company, this is expected to be the case in April 2022.

The company presented analyses on all patient-relevant outcomes for the first data cut-off, whereas it only presented analyses on overall survival and side effects for the second data cut-off. To make complete use of the available data, the results of the second data cut-off were used for overall survival and side effects, and the results of the first data cut-off were used for morbidity and health-related quality of life.

Uncertainties of study MM-007

Number of bortezomib cycles

According to the SPC of bortezomib [3], pretreated 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 control arm of the MM-007 study, treatment with bortezomib + dexamethasone could be administered for more than 8 cycles. This option was used for 39.6% of the patients in the control arm of the MM-007 study. The distribution of the number of cycles of the bortezomib treatment for these patients is presented in Table 8.

Table 8: Distribution of the bortezomib cycles in the control arm of the MM-007 study in patients who received more than 8 cycles

Number of bortezomib cycles (per interval)	**n (%) N = 270**	**Number of bortezomib cycles (cumulative)**	**n (%) N = 270**
9 to 12	30 (11.1)	≥ 9	107 (39.6)[a]
13 to 16	24 (8.9)	≥ 13	77 (28.5)[a]
17 to 20	12 (4.4)	≥ 17	53 (19.6)[a]
21 to 24	7 (2.6)	≥ 21	41 (15.2)[a]
25 to 28	8 (3.0)	≥ 25	34 (12.6)[a]
29 to 32	6 (2.2)	≥ 29	26 (9.6)[a]
33 to 36	2 (0.7)	≥ 33	20 (7.4)[a]
> 36	18 (6.7)	> 36	18 (6.7)
a: Institute's calculation. n: number of patients with the corresponding number of cycles; N: number of treated patients			

The company explained the number of cycles in the bortezomib + dexamethasone arm, stating that the MM-007 study had originally been planned as a US study only. According to the company, treatment in the bortezomib + dexamethasone arm was performed in compliance with the US prescribing information of bortezomib [9], which allows treatment for more than 8 cycles. According to the company, this treatment regimen also concurs with the ENDEAVOR study [10], which was used for the early benefit assessment of carfilzomib. However, the company did not provide any information on how such prolonged administration of bortezomib affects the effects in comparison with the ACT.

On the basis of the information in the dossier, the influence of bortezomib administration for more than 8 cycles is ultimately unclear. The guidelines of the DGHO do not provide any information on the duration of bortezomib therapy; it is recommended to treat patients up to 2 cycles after the best response [5].

Nevertheless, it is assumed that the possibility to administer bortezomib for more than 8 cycles does not question the relevance of the study. The described uncertainties were considered in the derivation of the added benefit, however, and led to a limitation in the certainty of conclusions (see Section 2.4.2).

Reduced dexamethasone dose in patients > 75 years

In the MM-007 study, patients aged > 75 years received dexamethasone at a dose of 10 mg/day instead of 20 mg/day. This dose is in line with the SPC for pomalidomide [6], but cannot be inferred from the SPC for bortezomib [3]. According to the SPC for bortezomib, the dexamethasone dose is 20 mg/day also for patients aged > 75 years. Neither the treatment of multiple myeloma, nor the dose reduction conducted in the MM-007 study can be inferred from the SPC for dexamethasone (e.g. [7]).

The reduced dose of dexamethasone affected 16.4% of the patients in the bortezomib + dexamethasone arm. The available results do not allow to estimate the effect of the deviation from the recommended dexamethasone dose on the overall result of the dossier assessment. However, it is assumed in the present situation that the reduced dexamethasone dose does not completely question the interpretability of the study; but it is a further aspect reducing the certainty of conclusions of the MM-007 study.

Planned duration of study MM-007

Table 9 shows the planned follow-up observation period of the patients for the individual outcomes.

Table 9: Planned duration of follow-up observation – RCT, direct comparison: pomalidomide + bortezomib + dexamethasone vs. bortezomib + dexamethasone

Study **Outcome category** **Outcome**	**Planned follow-up observation**
MM-007	
Mortality	
Overall survival	Every 3 months starting 28 days after the last dose of the study medication for at least 5 years after randomization of the last patient
Morbidity	
Symptoms (EORTC QLQ-C30 and EORTC QLQ-MY20 symptom scales)	No recording after the last dose of the study medication
Health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-MY20 functional scales)	No recording after the last dose of the study medication
Side effects	
All outcomes in the category "side effects"[a]	At least up to 28 days after the last dose of the study medication
a: Only study-/protocol-related adverse events were recorded in patients in the PFS follow-up phase. EORTC: European Organisation for Research and Treatment of Cancer; PFS: progression-free survival; QLQ-C30: Quality of Life Questionnaire Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20; RCT: randomized controlled trial; vs.: versus	

Follow-up observation until the end of the study (at least 5 years after randomization of the last patient) is planned for the outcome "overall survival". The observation periods for the outcomes on morbidity, health-related quality of life and side effects were systematically shortened, however, because they were only recorded for the time period of treatment with the study medication (plus 28 days for side effects). To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to record these outcomes over the total period of time, as was the case for "survival".

Patient characteristics

Table 10 shows the characteristics of the patients in the study included.

Table 10: Characteristics of the study population – RCT, direct comparison: pomalidomide + bortezomib + dexamethasone vs. bortezomib + dexamethasone

Study Characteristics Category	**Pomalidomide + bortezomib + dexamethasone**	**Bortezomib + dexamethasone**
MM-007	N[a] = 281	N[a] = 278
Age [years], mean (SD)	66 (10)	66 (10)
Sex [F/M], %	45/55	47/53
Ethnicity, n (%)		
Asian	14 (5.0)	8 (2.9)
Black or African American	8 (2.8)	13 (4.7)
White	237 (84.3)	234 (84.2)
Not recorded or reported	19 (6.8)	20 (7.2)
Other	3 (1.1)	3 (1.1)
ECOG PS, n (%)		
0	149 (53.0)	137 (49.3)
1	121 (43.1)	119 (42.8)
2	11 (3.9)	22 (7.9)
Type of myeloma (heavy chain type)[b], n (%)		
IgA	58 (20.6)	56 (20.1)
IgD	0 (0)	0 (0)
IgE	0 (0)	0 (0)
IgG	193 (68.7)	185 (66.5)
IgM	2 (0.7)	0 (0)
Undetected	25 (8.9)	28 (10.1)
Missing	3 (1.1)	9 (3.2)
ISS stage at baseline, n (%)		
I	149 (53.0)	138 (49.6)
II	85 (30.2)	90 (32.4)
III	47 (16.7)	50 (18.0)
Cytogenetic risk group		
High risk	61 (21.7)	49 (17.6)
Non-high risk	137 (48.8)	132 (47.5)
Missing or undeterminable	83 (29.5)	97 (34.9)
Disease duration: time between first diagnosis and randomization [years], median [min; max]	4.0 [0.2; 25.9]	4.3 [0.4; 21.8]
Number of prior anti-myeloma regimens, n (%)		
1	98 (34.9)	95 (34.2)
2	118 (42.0)	107 (38.5)
3	64 (22.8)	75 (27.0)
> 3	1 (0.4)	1 (0.4)

(continued)

Table 9: Planned duration of follow-up observation – RCT, direct comparison: pomalidomide + bortezomib + dexamethasone vs. bortezomib + dexamethasone (continued)

Study Characteristics Category	Pomalidomide + bortezomib + dexamethasone	Bortezomib + dexamethasone
MM-007	N[a] = 281	N[a] = 278
Prior anti-myeloma therapies, n (%)		
Systemic therapy	281 (100.0)	278 (100.0)
Lenalidomide	281 (100.0)	278 (100.0)
Bortezomib	201 (71.5)	203 (73.0)
Stem cell transplantation	161 (57.3)	163 (58.6)
Radiation	63 (22.4)	61 (21.9)
Surgery	17 (6.0)	22 (7.9)
Treatment refractoriness[c], n (%)		
To Lenalidomide	200 (71.2)	191 (68.7)
To bortezomib	24 (8.5)	32 (11.5)
Refractoriness to lenalidomide in the last prior anti-myeloma regimen	178 (63.3)	167 (60.1)
Treatment discontinuation[d], n (%)	224 (79.7)	251 (90.3)
Study discontinuation[d], n (%)	134 (47.7)	151 (54.3)

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: Typing based on immunoglobulin immunofixation in the serum (if available) or in the urine if serum unavailable.
c: Refractoriness is defined as the non-achievement of minimum response or progression of disease under treatment or progression within 60 days after the last dose. Refractoriness to a drug refers to the refractoriness at the last administration of the corresponding drug.
d: Second data cut-off from 15 September 2018.
ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; IgX: immunoglobulin X; ISS: International Staging System; M: male; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Patient characteristics were largely balanced in both treatment arms.

The mean age of the patients was 66 years. About 46% were women. The majority of the patients were white and in good general condition according to the ECOG PS. At baseline, about 80% of the patients were in the ISS stage of I or II and about 20% were in the high-risk cytogenetic risk group. Just under 60% of the patients had been treated with stem cell transplantation before enrolment. About 72% of the patients had received prior bortezomib. About 10% of the patients were refractory to bortezomib (see Section 2.7.4.1 of the full dossier assessment).

At the second data cut-off, 79.7% of the patients in the pomalidomide + bortezomib + dexamethasone arm and 90.3% of the patients in the bortezomib + dexamethasone arm had

discontinued treatment with the randomized study medication. The corresponding numbers for discontinuation of study participation were 47.7 versus 54.3%.

Observation periods and treatment durations in the MM-007 study

Table 11 shows the median and mean treatment durations of the patients and the median and mean observation periods for individual outcomes.

Table 11: Information on the course of the study – RCT, direct comparison: pomalidomide + bortezomib + dexamethasone vs. bortezomib + dexamethasone

Study **Duration of the study phase** **Outcome category**	**Pomalidomide + bortezomib + dexamethasone**	**Bortezomib + dexamethasone**
MM-007	N = 281	N = 278
Treatment duration [months][a]		
First data cut-off (26 Oct 2017)		
Median [min; max]	8.8 [0.3; 43.1][b]	4.9 [0.1; 37.8][b]
Mean (SD)	10.6 (7.7)[b]	6.8 (6.4)[b]
Second data cut-off (15 Sep 2018)		
Median [min; max]	9.5 [0.3; 53.6][b]	4.9 [0.1; 48.5][b]
Mean (SD)	13.3 (10.7)[b]	7.9 (8.5)[b]
Observation period [months]		
Overall survival		
First data cut-off (26 Oct 2017)		
Median [min; max]	16.2 [0.1; 57.4]	15.7 [0.0; 53.7]
Mean (SD)	17.3 (9.0)	16.4 (9.4)
Second data cut-off (15 Sep 2018)		
Median [min; max]	21.6 [0.1; 62.9]	20.5 [0.0; 64.4]
Mean (SD)	21.0 (12.3)	19.9 (12.6)
Morbidity, health-related quality of life[c]	ND	ND
Side effects		
First data cut-off (26 Oct 2017)		
Median [min; max]	ND	ND
Mean (SD)	11.2[b] (ND)	7.4[b] (ND)
Second data cut-off (15 Sep 2018)		
Median [min; max]	ND	ND
Mean (SD)	13.9[b] (ND)	8.5[b] (ND)

a: The values on treatment duration are based on the patients who received at least one dose of the study medication (278 vs. 270 patients).
b: Institute's calculation.
c: This information was neither available for the first nor for the second data cut-off.
max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

At the second data cut-off, the median treatment duration was 9.5 months in the pomalidomide + bortezomib + dexamethasone arm and 4.9 months in the bortezomib + dexamethasone arm. This difference is not reflected in the median observation period for overall survival (21.6 versus 20.5 months).

The mean observation period for side effects was slightly longer than the mean treatment duration.

The company's dossier contained no information on the observation period of morbidity and health-related quality of life.

Subsequent treatment of multiple myeloma in the MM-007 study

Table 12 shows the subsequent treatments for multiple myeloma in the MM-007 study.

Table 12: Subsequent treatments of multiple myeloma (≥ 5% of the patients in ≥ 1 treatment arm) – RCT, direct comparison: pomalidomide + bortezomib + dexamethasone vs. bortezomib + dexamethasone

Study	**Patients with event n (%)**	
Drug class[a] **Drug[a]**	**Pomalidomide + bortezomib + dexamethasone** **N = 281**	**Bortezomib + dexamethasone** **N = 278**
MM-007		
Subsequent treatments (second data cut-off [15 Sep 2018])	151 (53.7)	198 (71.2)
Corticosteroids	113 (40.2)	172 (61.9)
Dexamethasone	104 (37.0)	161 (57.9)
Immunomodulatory drugs	68 (24.2)	165 (59.4)
Pomalidomide	32 (11.4)	133 (47.8)
Lenalidomide	30 (10.7)	51 (18.3)
Thalidomide	15 (5.3)	12 (4.3)
Proteasome inhibitors	78 (27.8)	94 (33.8)
Carfilzomib	47 (16.7)	52 (18.7)
Bortezomib	40 (14.2)	42 (15.1)
Monoclonal antibodies	81 (28.8)	75 (27.0)
Daratumumab	63 (22.4)	50 (18.0)
Elotuzumab	14 (5.0)	18 (6.5)
Alkylating drugs	73 (26.0)	75 (27.0)
Cyclophosphamide	47 (16.7)	54 (19.4)
Melphalan	20 (7.1)	15 (5.4)
Bendamustine	15 (5.3)	15 (5.4)

a: WHO Drug Dictionary, Version March 2018.

n: number of patients with (at least one) drug; N: number of analysed patients; RCT: randomized controlled trial; vs.: versus; WHO: World Health Organization

The proportion of patients with subsequent treatment of multiple myeloma in the MM-007 study was lower in the pomalidomide + bortezomib + dexamethasone arm than in the bortezomib + dexamethasone arm. Regarding individual drugs, there were differences between the treatment arms, particularly due to subsequent treatment with pomalidomide (11.4% versus 47.8% of the patients). The company considered the risk of bias for the results of the outcome "overall survival" as high due to the high proportion of pomalidomide as subsequent therapy in the control arm. Pomalidomide is an approved treatment option for the patients in the therapeutic indication of the present research question, however. Hence, administration of pomalidomide as subsequent therapy is not to be considered treatment switching in the sense of [8] (see also Section 2.7.4.2 of the full dossier assessment).

Risk of bias across outcomes (study level)

Table 13 shows the risk of bias across outcomes (risk of bias at study level).

Table 13: Risk of bias across outcomes (study level) – RCT, direct comparison: pomalidomide + 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			
MM-007	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias across outcomes was rated as low for the MM-007 study. This concurs with the company's assessment.

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

2.4 Results on added benefit

2.4.1 Outcomes included

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

- Mortality
  - overall survival

- Morbidity
  - symptoms measured with the EORTC QLQ-C30 and QLQ-MY20 symptom scales
- Health-related quality of life
  - health-related quality of life measured with the EORTC QLQ-C30 and QLQ-MY20 functional scales
- Side effects
  - SAEs
  - discontinuation due to AEs
  - severe AEs (CTCAE grade ≥ 3)
  - peripheral neuropathy (SMQ, AEs)
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.7.4.3 of the full dossier assessment).

Table 14 shows for which outcomes data were available in the study included.

Table 14: Matrix of outcomes – RCT, direct comparison: pomalidomide + bortezomib + dexamethasone vs. bortezomib + dexamethasone

Study	Outcomes							
	Overall survival	**Symptoms (EORTC QLQ-C30 and QLQ-MY20 symptom scales)**	**Health-related quality of life (EORTC QLQ-C30 and QLQ-MY20 functional scales)**	**SAEs**	**Discontinuation due to AEs (≥ 1 drug component)**	**Severe AEs (CTCAE grade ≥ 3)**	**Peripheral neuropathy (SMQ, AE)**	**Further specific AEs[a]**
MM-007	Yes[b]	Yes[c]	Yes[c]	Yes[b]	Yes[b]	Yes[b]	Yes[b]	Yes[b]

a: The following events are considered (MedDRA coding): "venous thromboembolic event (SMQ, AE)", "neutropenia (PT, severe AEs [CTCAE grade ≥ 3])".
b: First data cut-off (26 October 2017) and second data cut-off (15 September 2018), the second data cut-off is considered.
c: First data cut-off (26 October 2017)
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; vs.: versus

2.4.2 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: pomalidomide + bortezomib + dexamethasone vs. bortezomib + dexamethasone

Study		Outcomes							
	Study level	Overall survival[a]	Symptoms (EORTC QLQ-C30 and QLQ-MY20 symptom scales)[b]	Health-related quality of life (EORTC QLQ-C30 and QLQ-MY20 functional scales)[b]	SAEs[a]	Discontinuation due to AEs (≥ 1 drug component)[a]	Severe AEs (CTCAE grade ≥ 3)[a]	Peripheral neuropathy (SMQ, AE)[a]	Further specific AEs[a, c]
MM-007	L	L	H[d, e]	H[d, e]	H[e]	H[d]	H[e, f]	H[d, e]	H[d, e]

a: Second data cut off: 15 September 2018 (not prespecified, conducted in the framework of the extension of approval of pomalidomide).
b: First data cut-off: 26 October 2017 (prespecified), the company presented no analyses on the second data cut-off.
c: The following events are considered (MedDRA coding): "venous thromboembolic event (SMQ, AE)", "neutropenia (PT, severe AEs [CTCAE grade 3 and 4])".
d: Lack of blinding in subjective recording of outcomes.
e: Incomplete observations for potentially informative reasons, differences in the observation periods between the treatment groups.
f: Restricted certainty of results due to competing events (see Section 2.7.4.2 of the full dossier assessment).
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; vs.: versus

The risk of bias of the result on the outcome "overall survival" was rated as low. This deviates from the assessment of the company, which rated the risk of bias for health-related quality of life as high due to the subsequent treatments. Subsequent treatments are discussed in Section 2.3.2.

The risk of bias of the results for the outcomes on symptoms (EORTC QLQ-C30 and QLQ-MY20 symptom scales) and health-related quality of life (EORTC QLQ-C30 and QLQ-MY20 functional scales) was rated as high due to the lack of blinding in subjective recording of outcomes and potentially informative censoring (see Section 2.7.4.2 of the full dossier assessment). The company also rated the risk of bias as high for these results.

Due to potentially informative censoring, the risk of bias of the results for the outcomes "SAEs", and "severe AEs (CTCAE grade ≥ 3)" was rated as high. This concurs with the company's assessment. The company assumed an additional high risk of bias due to lack of blinding, however. This view was not shared (see Section 2.7.4.2 of the full dossier assessment).

The risk of bias of the result for the outcome "discontinuation due to AEs (≥ 1 drug component)" was rated as high due to lack of blinding in subjective recording of outcomes (see Section 2.7.4.2 of the full dossier assessment). This concurs with the company's assessment. The company additionally assumed potentially informative censoring in this outcome, however. This view was not shared. However, there was restricted certainty of results due to potentially competing events (see Section 2.7.4.2 of the full dossier assessment).

The company did not assess the risk of bias for the results of the specific AEs "peripheral neuropathy (SMQ, AE)", "venous thromboembolic event (SMQ, AE)", "neutropenia (PT, severe AEs [CTCAE grade 3 and 4]). Due to the lack of blinding (AEs) and potentially informative censoring (AEs, SAEs, severe AEs [CTCAE grade ≥ 3]), the risk of bias was rated as high in each case.

Overall assessment of the certainty of conclusions

The open-label RCT MM-007 was available for the assessment. The risk of bias of the results was rated as high for all outcomes except overall survival.

As described in Section 2.3.2, the use of bortezomib for more than 8 cycles and the dexamethasone dose in patients aged > 75 years in the comparator arm of the MM-007 study do not comply with the SPC for bortezomib [3]. This additionally reduces the certainty of conclusions of the study.

Hence, at most hints, e.g. of an added benefit, can be derived from the MM-007 study. The outcome-specific assessment can deviate from this.

2.4.3 Results

Table 16 summarizes the results for the comparison of pomalidomide + bortezomib + dexamethasone with bortezomib + dexamethasone in patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. Kaplan-Meier curves on the outcomes included are presented in Appendix A and those on subgroup analyses in Appendix B of the full dossier assessment. Results on common AEs are presented in Appendix C of the full dossier assessment.

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

Study Outcome category Outcome	Pomalidomide + bortezomib + dexamethasone		Bortezomib + dexamethasone		Pomalidomide + 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
MM-007					
Mortality (second data cut-off [15 September 2018])					
Overall survival	281	40.5 [29.8; NC] 116 (41.3)	278	30.5 [24.6; 35.9] 126 (45.3)	0.91 [0.70; 1.18]; 0.476[a]
Morbidity (first data cut-off [26 October 2017])					
Symptoms (EORTC QLQ-C30 symptom scales)[b]					
Fatigue	240[c]	1.6 [1.4; 2.1] 204 (85.0)	209[c]	1.7 [1.4; 2.1] 156 (74.6)	1.13 [0.92; 1.40]; 0.241[d]
Nausea and vomiting	240[c]	10.6 [7.2; 14.8] 111 (46.3)	209[c]	13.9 [11.0; NC] 76 (36.4)	1.05 [0.78; 1.41]; 0.733[d]
Pain	240[c]	3.6 [2.9; 5.7] 157 (65.4)	209[c]	3.4 [2.8; 5.1] 120 (57.4)	0.97 [0.76; 1.23]; 0.782[d]
Dyspnoea	240[c]	3.5 [2.8; 4.2] 156 (65.0)	209[c]	3.5 [2.9; 4.9] 111 (53.1)	1.14 [0.89; 1.45]; 0.310[d]
Insomnia	240[c]	4.5 [3.3; 6.1] 144 (60.0)	209[c]	3.5 [2.8; 5.6] 113 (54.1)	0.94 [0.73; 1.20]; 0.598[d]
Appetite loss	239[c]	4.8 [3.8; 6.0] 144 (60.3)	209[c]	6.5 [4.5; 9.3] 94 (45.0)	1.21 [0.93; 1.58]; 0.152[d]
Constipation	240[c]	2.9 [2.2; 4.3] 154 (64.2)	209[c]	3.7 [2.8; 5.4] 108 (51.7)	1.32 [1.03; 1.69]; 0.030[d]
Diarrhoea	239[c]	9.2 [6.0; 12.8] 118 (49.4)	209[c]	6.8 [4.5; 9.9] 90 (43.1)	0.96 [0.72; 1.26]; 0.752[d]
Symptoms (EORTC QLQ-MY20 symptom scales)[b]					
Disease-related symptoms	238[c]	7.9 [5.5; 10.2] 123 (51.7)	207[c]	11.0 [5.4; 15.2] 88 (42.5)	1.08 [0.82; 1.42]; 0.598[d]
Side effects	238[c]	3.0 [2.4; 3.6] 175 (73.5)	207[c]	3.0 [2.7; 3.6] 129 (62.3)	1.07 [0.85; 1.35]; 0.548[d]

(continued)

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

Study Outcome category Outcome	Pomalidomide + bortezomib + dexamethasone		Bortezomib + dexamethasone		Pomalidomide + 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
Health-related quality of life (first data cut-off: 26 October 2017)					
EORTC QLQ-C30 functional scales[b]					
Global health status	240[c]	3.1 [2.3; 4.0] 159 (66.3)	209[c]	3.4 [2.7; 4.2] 124 (59.3)	1.17 [0.92; 1.48]; 0.206[d]
Physical functioning	240[c]	3.3 [2.8; 4.3] 163 (67.9)	209[c]	3.6 [3.0; 4.8] 117 (56.0)	1.12 [0.88; 1.42]; 0.365[d]
Role functioning	240[c]	2.8 [2.2; 3.0] 183 (76.3)	209[c]	2.6 [2.1; 3.1] 141 (67.5)	1.00 [0.80; 1.25]; 0.987[d]
Cognitive functioning	240[c]	3.6 [2.8; 5.1] 156 (65.0)	209[c]	4.9 [3.2; 8.6] 104 (49.8)	1.22 [0.95; 1.57]; 0.117[d]
Emotional functioning	240[c]	4.5 [3.5; 5.5] 156 (65.0)	209[c]	5.1 [4.0; 7.8] 108 (51.7)	1.12 [0.87; 1.43]; 0.371[d]
Social functioning	240[c]	2.8 [2.3; 3.5] 178 (74.2)	209[c]	2.8 [2.1; 3.9] 131 (62.7)	1.12 [0.90; 1.41]; 0.313[d]
EORTC QLQ-MY20 functional scales[b]					
Future perspective	238[c]	4.9 [3.1; 7.2] 143 (60.1)	207[c]	4.4 [3.5; 7.0] 108 (52.2)	0.98 [0.76; 1.26]; 0.861[d]
Body image	238[c]	5.0 [3.9; 8.1] 131 (55.0)	207[c]	6.9 [4.2; 9.9] 101 (48.8)	0.98 [0.75; 1.27]; 0.854[d]
Side effects (second data cut-off [15 September 2018])					
AEs (supplementary information)	278[e]	0.2 [0.1; 0.2] 278 (100.0)	270[e]	0.3 [0.1; 0.3] 264 (97.8)	–
SAEs	278[e]	6.3 [4.3; 10.5] 169 (60.8)	270[e]	19.1 [6.1; NC] 116 (43.0)	1.28 [1.01; 1.63]; 0.039[f]
Severe AEs (CTCAE grade ≥ 3)	278[e]	0.8 [0.7; 1.2] 258 (92.8)	270[e]	1.7 [1.1; 2.2] 193 (71.5)	1.56 [1.30; 1.88]; < 0.001[f]
Discontinuation due to AEs (≥ 1 drug component)	278[e]	37.3 [31.3; NC] 83 (29.9)	270[e]	NA 52 (19.3)	1.27 [0.90; 1.80]; 0.173[f]

(continued)

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

Study Outcome category Outcome	Pomalidomide + bortezomib + dexamethasone		Bortezomib + dexamethasone		Pomalidomide + 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
Specific AEs					
Peripheral neuropathy (SMQ, AE)	278	4.4 [3.6; 5.9] 154 (55.4)	270	5.8 [4.4; NC] 117 (43.3)	1.21 [0.95; 1.54]; 0.115[f]
Venous thromboembolic event (SMQ, AE)	278	NA 32 (11.5)	270	NA 7 (2.6)	3.27 [1.44; 7.44]; 0.005[f]
Neutropenia (PT, severe AEs [CTCAE grade ≥ 3])	278	18.0 [14.3; 25.6] 126 (45.3)	270	NA 24 (8.9)	5.27 [3.40; 8.17]; < 0.001[f]

a: Cox proportional hazards model adjusted by the stratification factors age, number of prior anti-myeloma regimens and beta-2 microglobulin level at screening.

b: Time to deterioration by at least 10 points from baseline.

c: Study participants for whom a baseline value and at least one post-baseline value were available were taken into account (HRQoL evaluable population).

d: Cox proportional hazards model adjusted by baseline score and the stratification factors age, number of prior anti-myeloma regimens and beta-2 microglobulin level at screening.

e: Safety population.

f: Cox proportional hazards model, stratified log-rank test.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; HRQoL: health-related quality of life; ITT: intention to treat; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with event; N: number of analysed patients (ITT population); NA: not achieved; NC: not calculable; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; vs.: versus

The open-label RCT MM-007 was available for the assessment. The risk of bias of the results was rated as high for all outcomes except overall survival. The certainty of conclusions of the MM-007 study was additionally reduced due to the described uncertainty regarding the use of bortezomib and dexamethasone in the comparator arm (see Section 2.4.2). At most hints, e.g. of an added benefit, can therefore be derived from the results of the MM-007 study. The outcome-specific certainty of conclusions of the results may not be downgraded, however (see description of the results below).

Mortality

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

This deviates from the assessment of the company, which derived an indication of an added benefit on the basis of the results of an exploratory analysis (adjustment by subsequent therapies). As shown in Section 2.7.4.2 of the full dossier assessment, these results are not usable.

Morbidity

Symptoms (EORTC QLQ-C30 and QLQ-MY20 symptom scales)

Symptom outcomes were recorded with the symptom scales of the EORTC QLQ-C30 and QLQ-MY20. The time to first deterioration by ≥ 10 points was considered in each case.

A statistically significant difference to the disadvantage of pomalidomide + bortezomib + dexamethasone was shown for the outcome "constipation". For an outcome of the category of non-serious/non-severe symptoms/late complications, the difference was no more than marginal, however. This resulted in no hint of lesser benefit or added benefit of pomalidomide + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone; lesser benefit or added benefit is therefore not proven.

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

These assessments correspond to the assessments of the company.

Health-related quality of life

Outcomes of health-related quality of life were recorded with the functional scales of the EORTC QLQ-C30 and QLQ-MY20. The time to first deterioration by ≥ 10 points was considered in each case.

Physical functioning, role functioning, cognitive functioning, emotional functioning, future perspective and body image

No statistically significant differences between the treatment arms were shown for the outcomes "physical functioning", "role functioning", "cognitive functioning", "emotional functioning", "future perspective" and "body image". In each case, this resulted in no hint of an added benefit of pomalidomide + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone; an added benefit is therefore not proven.

This assessment corresponds to the assessment of the company.

Global health status and social functioning

No statistically significant difference between the treatment arms was shown for each of the outcomes "global health status" and "social functioning".

There was an effect modification by the characteristic "ISS stage" for the outcome "global health status", however (see Section 2.4.4). Hence, for patients with ISS stage I or II, there was no hint of an added benefit of pomalidomide + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone; an added benefit is therefore not proven. For patients with ISS stage III, in contrast, there was a hint of an added benefit of pomalidomide + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone.

There was an effect modification by the characteristic "number of prior anti-myeloma regimens" for the outcome "social functioning" (see Section 2.4.4). For patients with > 1 regimen, there was no hint of an added benefit of pomalidomide + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone; an added benefit is therefore not proven. For patients with 1 regimen, in contrast, there was a hint of greater harm of pomalidomide + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone.

This deviates from the assessment of the company, which did not derive different added benefits for different subgroups and therefore found no indication of an added benefit for either outcome.

Side effects

Serious adverse events

A statistically significant difference to the disadvantage of pomalidomide + bortezomib + dexamethasone was shown for the outcome "SAEs". This resulted in a hint of greater harm of pomalidomide + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone.

This assessment deviates from the assessment of the company, which, on the basis of the rate ratio, derived no indication of greater or lesser benefit.

Severe adverse events (CTCAE grade ≥ 3)

A statistically significant difference to the disadvantage of pomalidomide + bortezomib + dexamethasone was shown for the outcome "severe AEs (CTCAE grade ≥ 3)". This resulted in a hint of greater harm of pomalidomide + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone.

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

Discontinuation due to adverse events (≥ 1 drug component)

There was no statistically significant difference between the treatment arms for the outcome "discontinuation due to AEs (≥ 1 drug component)". This resulted in no hint of greater or lesser harm from pomalidomide + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone; greater or lesser harm is therefore not proven.

This assessment corresponds to the assessment of the company.

Specific adverse events

Peripheral neuropathy (SMQ, AE)

There was no statistically significant difference between the treatment arms for the outcome "peripheral neuropathy (SMQ, AE)". This resulted in no hint of greater or lesser harm from pomalidomide + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone; greater or lesser harm is therefore not proven.

This assessment corresponds to the assessment of the company.

Venous thromboembolic event (SMQ, AE)

A statistically significant difference to the disadvantage of pomalidomide + bortezomib + dexamethasone was shown for the outcome "venous thromboembolic event (SMQ, AE)". This resulted in a hint of greater harm of pomalidomide + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone.

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

Neutropenia (PT, severe AEs [CTCAE grade ≥ 3])

A statistically significant difference to the disadvantage of pomalidomide + bortezomib + dexamethasone was shown for the outcome "neutropenia (PT, severe AEs [CTCAE grade ≥ 3])". There was a high certainty of conclusions despite the high risk of bias because an effect in the present magnitude cannot be explained by different observation periods in the treatment arms alone. In addition, the effect occurred already early in the course of the study. Hence, an indication of greater harm from pomalidomide + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone was derived for this outcome.

This assessment largely corresponds to the assessment of the company, which derived an indication of lesser benefit.

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics were considered in the present assessment:

- age (≤ 75 years versus > 75 years)
- sex (female versus male)
- ethnicity (white versus non-white)
- number of prior anti-myeloma regimens (1 versus > 1)
- ISS stage (I versus II versus III)
- prior stem cell transplantation (yes versus no)

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

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

The subgroup analyses of side effects presented by the company are not interpretable as they were not performed on the basis of event time analyses. Hence, effect modifications for side effects cannot be assessed.

The subgroup results of pomalidomide + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone are summarized in Table 17.

Table 17: Subgroups (health-related quality of life) – RCT, direct comparison: pomalidomide + bortezomib + dexamethasone vs. bortezomib + dexamethasone

Study **Outcome** **Characteristic** **Subgroup**	**Pomalidomide + bortezomib + dexamethasone**		**Bortezomib + dexamethasone**		**Pomalidomide + bortezomib + dexamethasone vs. bortezomib + dexamethasone**	
	N[a]	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N[a]**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]**	**p-value[b]**
MM-007						
Morbidity (first data cut-off [26 October 2017])						
EORTC QLQ-C30 functional scales[c]						
Global health status						
ISS stage						
I	*128*	*2.4 [2.1; 3.3]* *92 (71.9)*	*109*	*3.6 [2.8; 5.0]* *66 (60.6)*	*1.19 [0.87; 1.64]*	*0.278*
II	*74*	*2.8 [1.6; 5.6]* *48 (64.9)*	*67*	*3.3 [2.1; NC]* *35 (52.2)*	*1.11 [0.72; 1.71]*	*0.647*
III	*38*	*5.3 [3.8; NC]* *19 (50.0)*	*33*	*1.5 [0.9; 4.2]* *23 (69.7)*	*0.47 [0.26; 0.87]*	*0.015*
Total					*Interaction:*	*0.027[e]*
Global health status						
ISS stage						
I or II[d]	202	ND 140 (69.3)	176	ND 101 (57.4)	1.16 [0.90; 1.50]	0.251
III	38	5.3 [3.8; NC] 19 (50.0)	33	1.5 [0.9; 4.2] 23 (69.7)	0.47 [0.26; 0.87]	0.015
Total I or II vs. III					Interaction:	0.007[d]
Social functioning						
Number of prior anti-myeloma regimens						
1	86	2.8 [2.2; 4.7] 69 (80.2)	71	5.5 [2.8; 13.0] 37 (52.1)	1.63 [1.09; 2.43];	0.016
> 1	154	2.8 [2.2; 3.7] 109 (70.8)	138	2.2 [1.6; 3.0] 94 (68.1)	0.88 [0.66; 1.16];	0.351
Total					Interaction:	0.012[e]

(continued)

Table 17: Subgroups (health-related quality of life) – RCT, direct comparison: pomalidomide + bortezomib + dexamethasone vs. bortezomib + dexamethasone (continued)

a: Study participants for whom a baseline value and at least one post-baseline value were available were taken into account (HRQoL evaluable population).
b: Cox proportional hazards model with treatment arm and baseline score as covariates, adjusted by the stratification factors age, number of prior anti-myeloma regimens and beta-2 microglobulin level at screening.
c: Time to clinically relevant deterioration by at least 10 points from baseline.
d: Institute's calculation: meta-analysis of the subgroup results for ISS stage I and II (fixed-effect model).
e: Cox model with terms for the subgroup, the treatment group and the subgroup-treatment interaction.
CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; HRQoL: health-related quality of life; ISS: International Staging System; n: number of patients with event; N: number of analysed patients; NC: not calculable; ND: no data; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; vs.: versus

EORTC QLQ-C30 functional scales

Global health status

For the outcome "global health status", there was an effect modification (interaction test: p = 0.027) by the characteristic ISS stage with the subgroups I, II and III. In the present data situation, the subgroups with homogeneous effects (ISS stage I and II) were aggregated with a fixed-effect model due to the identical study (see Figure 31 in Appendix B of the full dossier assessment). The interaction test between the subgroup results by the characteristic ISS stage (aggregated subgroup from ISS stage I and II versus ISS stage III) produced a p-value of 0.007.

There was no statistically significant difference between the treatment arms for the aggregated subgroup of ISS stage I or II. A statistically significant difference in favour of pomalidomide + bortezomib + dexamethasone was shown for the subgroup of patients in ISS stage III. Hence, for patients with ISS stage I or II, there was no hint of an added benefit of pomalidomide + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone; an added benefit is therefore not proven. For patients with ISS stage III, in contrast, there was a hint of an added benefit of pomalidomide + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone.

This deviates from the company, which did not derive different added benefits for different subgroups.

Social functioning

There was an effect modification by the number of prior anti-myeloma regimens for the outcome "social functioning". There was no statistically significant difference between the treatment arms for the subgroup with > 1 prior regimen. For patients who had received treatment with 1 prior regimen, however, there was a statistically significant difference to the disadvantage of pomalidomide + bortezomib + dexamethasone. For patients with > 1 regimen, there was no hint of an added benefit of pomalidomide + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone; an added benefit is therefore not proven. For

patients with 1 regimen, in contrast, there was a hint of greater harm of pomalidomide + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone.

This deviates from the company, which did not derive different added benefits for different subgroups.

2.5 Probability and extent of added benefit

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

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

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 18).

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

It could not be inferred from the dossier for all outcomes considered in the present benefit assessment whether they were serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

EORTC QLQ-C30 (symptom scales): constipation

The dossier contained no information on the allocation of the severity category for the outcome "constipation" of the EORTC QLQ-C30 (symptom scales). Therefore, the outcome "constipation" was allocated to the outcome category "non-serious/non-severe symptoms/late complications".

Specific AE "venous thromboembolic event (SMQ, AE)"

The specific AE "venous thromboembolic event (SMQ, AE)" was allocated to the category of serious/severe side effects as the event was serious/severe (CTCAE grade ≥ 3) in > 50% of the affected patients.

Table 18: Extent of added benefit at outcome level: pomalidomide + bortezomib + dexamethasone vs. bortezomib + dexamethasone

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pomalidomide + bortezomib + dexamethasone vs. bortezomib + dexamethasone** **Median time to event (months)** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	40.5 vs. 30.5 HR: 0.91 [0.70; 1.18] p = 0.476	Lesser benefit/added benefit not proven
Morbidity		
Symptoms (EORTC QLQ-C30 – symptom scales), time to deterioration by ≥ 10 points		
Fatigue	1.6 vs. 1.7 HR: 1.13 [0.92; 1.40] p = 0.241	Lesser benefit/added benefit not proven
Nausea and vomiting	10.6 vs. 13.9 HR: 1.05 [0.78; 1.41] p = 0.733	Lesser benefit/added benefit not proven
Pain	3.6 vs. 3.4 HR: 0.97 [0.76; 1.23] p = 0.782	Lesser benefit/added benefit not proven
Dyspnoea	3.5 vs. 3.5 HR: 1.14 [0.89; 1.45] p = 0.310	Lesser benefit/added benefit not proven
Insomnia	4.5 vs. 3.5 HR: 0.94 [0.73; 1.20] p = 0.598	Lesser benefit/added benefit not proven
Appetite loss	4.8 vs. 6.5 HR: 1.21 [0.93; 1.58] p = 0.152	Lesser benefit/added benefit not proven
Constipation	2.9 vs. 3.7 HR: 1.32 [1.03; 1.69] HR: 0.76 [0.59; 0.97][c] p = 0.030	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[d]
Diarrhoea	9.2 vs. 6.8 HR: 0.96 [0.72; 1.26] p = 0.752	Lesser benefit/added benefit not proven

(continued)

Table 18: Extent of added benefit at outcome level: pomalidomide + bortezomib + dexamethasone vs. bortezomib + dexamethasone (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pomalidomide + bortezomib + dexamethasone vs. bortezomib + dexamethasone** **Median time to event (months)** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Symptoms (EORTC QLQ-MY20 – symptom scales), time to deterioration by ≥ 10 points		
Disease-related symptoms	7.9 vs. 11.0 HR: 1.08 [0.82; 1.42] p = 0.598	Lesser benefit/added benefit not proven
Side effects	3.0 vs. 3.0 HR: 1.07 [0.85; 1.35] p = 0.548	Lesser benefit/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 functional scales, time to deterioration by ≥ 10 points		
Global health status ISS stage I or II	ND vs. ND HR: 1.16 [0.90; 1.50] p = 0.251	Lesser benefit/added benefit not proven
III	5.3 vs. 1.5 HR: 0.47 [0.26; 0.87] p = 0.015 probability: “hint”	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ Added benefit, extent: “considerable”
Physical functioning	3.3 vs. 3.6 HR: 1.12 [0.88; 1.42] p = 0.365	Lesser benefit/added benefit not proven
Role functioning	2.8 vs. 2.6 HR: 1.00 [0.80; 1.25] p = 0.987	Lesser benefit/added benefit not proven
Cognitive functioning	3.6 vs. 4.9 HR: 1.22 [0.95; 1.57] p = 0.117	Lesser benefit/added benefit not proven
Emotional functioning	4.5 vs. 5.1 HR: 1.12 [0.87; 1.43] p = 0.371	Lesser benefit/added benefit not proven

(continued)

Table 18: Extent of added benefit at outcome level: pomalidomide + bortezomib + dexamethasone vs. bortezomib + dexamethasone (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pomalidomide + bortezomib + dexamethasone vs. bortezomib + dexamethasone** **Median time to event (months)** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Social functioning		
Number of prior anti-myeloma regimens		
1	2.8 vs. 5.5 HR: 1.63 [1.09; 2.43] HR: 0.61 [0.41; 0.92][c] p = 0.016 probability: "hint"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ lesser benefit, extent: "minor"
> 1	2.8 vs. 2.2 HR: 0.88 [0.66; 1.16] p = 0.351	Lesser benefit/added benefit not proven
EORTC QLQ-MY20 – functional scales, time to deterioration by ≥ 10 points		
Future perspective	4.9 vs. 4.4 HR: 0.98 [0.76; 1.26] p = 0.861	Lesser benefit/added benefit not proven
Body image	5.0 vs. 6.9 HR: 0.98 [0.75; 1.27] p = 0.854	Lesser benefit/added benefit not proven
Side effects, time to first event		
SAEs	6.3 vs. 19.1 HR: 1.28 [1.01; 1.63] HR: 0.78 [0.61; 0.99][c] p = 0.039 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: "minor"
Severe AEs (CTCAE grade ≥ 3)	0.8 vs. 1.7 HR: 1.56 [1.30; 1.88] HR: 0.64 [0.53; 0.77][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 (≥ 1 drug component)	37.3 vs. NA HR: 1.27 [0.90; 1.80] p = 0.173	Greater/lesser harm not proven

(continued)

Table 18: Extent of added benefit at outcome level: pomalidomide + bortezomib + dexamethasone vs. bortezomib + dexamethasone (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pomalidomide + bortezomib + dexamethasone vs. bortezomib + dexamethasone** **Median time to event (months)** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Specific AEs		
Peripheral neuropathy (SMQ, AE)	4.4 vs. 5.8 HR: 1.21 [0.95; 1.54] p = 0.115	Greater/lesser harm not proven
Venous thromboembolic event (SMQ, AE)	NA vs. NA HR: 3.27 [1.44; 7.44] HR: 0.31 [0.13; 0.69][c] p = 0.005 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% greater harm, extent: "major"
Neutropenia (PT, severe AEs [CTCAE grade ≥ 3])	18.0 vs. NA HR: 5.27 [3.40; 8.17] HR: 0.19 [0.12; 0.29][c] p < 0.001 Probability: "indication"	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: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
d: The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; ISS: International Staging System; MedDRA: Medical Dictionary for Regulatory Activities; NA: not achieved; ND: no data; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20; SAE: serious adverse event; SMQ: Standardized MedDRA Query; vs.: versus

2.5.2 Overall conclusion on added benefit

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

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

Positive effects	**Negative effects**
Health-related quality of life ▪ EORTC QLQ-C30 functional scales, global health status ▫ ISS stage = III hint of added benefit – extent: “considerable”	Health-related quality of life ▪ EORTC QLQ-C30 – functional scales, social functioning ▫ number of prior anti-myeloma regimens = 1 hint of lesser benefit – extent: “minor”
–	Serious/severe side effects ▪ SAEs: hint of greater harm – extent: “minor” ▪ severe AEs (CTCAE grade ≥ 3): hint of greater harm – extent: “considerable”, including ▫ neutropenia (PT, severe AEs [CTCAE grade ≥ 3]): indication of greater harm – extent: “major” ▪ AEs, including ▫ venous thromboembolic event (SMQ, AE): hint of greater harm – extent “major”
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; ISS: International Staging System; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; SMQ: Standardized MedDRA Query; SAE: serious adverse event	

In the overall consideration, based on the total population, there are only negative effects of pomalidomide + bortezomib + dexamethasone compared with bortezomib + dexamethasone with different probabilities (hints or indication) and different extents (minor to major) for several side effect outcomes that can be allocated to the outcome category of serious/severe side effects.

For the outcomes of health-related quality of life, a positive effect was shown for the subgroup of patients in ISS stage III (hint of considerable added benefit in the EORTC QLQ-C30 – functional scales, global health status), and a negative effect for the subgroup of patients with one prior anti-myeloma regimen (hint of lesser benefit of minor extent in the EORTC QLQ-C30 – functional scales, social functioning).

For the patients in ISS stage III, the negative effects from side effects outweighed the positive effect in global health status. Overall, this resulted in lesser benefit for the total population. Considering the certainty of conclusions of the superordinate outcomes of side effects (SAEs and severe AEs [CTCAE grade ≥ 3]), a hint of lesser benefit was derived.

In summary, there is a hint of lesser benefit of pomalidomide + bortezomib + dexamethasone versus bortezomib + dexamethasone for patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide.

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

Table 20: Pomalidomide – 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 prior treatment regimen including lenalidomide	▪ 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	Hint of lesser benefit
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The assessment described above deviates from that of the company, which derived an indication of a non-quantifiable added benefit for pomalidomide + bortezomib + dexamethasone.

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

2.6 List of included studies

Celgene. Eine multizentrische, randomisierte offene Phase-III-Studie zum Vergleich der Wirksamkeit und Sicherheit von Pomalidomid (POM), Bortezomib (BTZ) und niedrigdosiertem Dexamethason (LD-DEX) gegenüber Bortezomib und niedrigdosiertem Dexamethason bei Studienteilnehmern mit rezidiviertem oder refraktärem Multiplem Myelom (MM) [online]. In: Deutsches Register Klinischer Studien. [Accessed: 19.06.2019]. URL: http://www.drks.de/DRKS00008025.

Celgene. A phase 3, multicenter, randomized, open-label study to compare the efficacy and safety of pomalidomide, bortezomib and low-dose dexamethasone versus bortezomib and low-dose dexamethasone in subjects with relapsed or refractory multiple myeloma [online]. In: EU Clinical Trials Register. [Accessed: 19.06.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-000268-17.

Celgene. Safety and efficacy of pomalidomide, bortezomib and low-dose dexamethasone in subjects with relapsed or refractory multiple myeloma (OPTIMISMM): study details [online]. In: ClinicalTrials.gov. 17.04.2019 [Accessed: 19.06.2019]. URL: https://ClinicalTrials.gov/show/NCT01734928.

Celgene. A phase 3, multicenter, randomized, open-label study to compare the efficacy and safety of pomalidomide, bortezomib and low-dose dexamethasone versus bortezomib and low-dose dexamethasone in subjects with relapsed or refractory multiple myeloma: study CC-4047-MM-007; clinical study report [unpublished]. 2018.

Celgene. A phase 3, multicenter, randomized, open-label study to compare the efficacy and safety of pomalidomide, bortezomib and low-dose dexamethasone versus bortezomib and low-dose dexamethasone in subjects with relapsed or refractory multiple myeloma: study CC-4047-MM-007; Zusatzanalysen [unpublished]. 2019.

Richardson PG, Oriol A, Beksac M, Liberati AM, Galli M, Schjesvold F et al. Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial. Lancet Oncol 2019; 20(6): 781-794.

References for English extract

Please see full dossier assessment for full reference list.

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

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The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a19-50-pomalidomide-multiple-myeloma-benefit-assessment-according-to-35a-social-code-book-v.12446.html.