IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A17-40

Daratumumab (multiple myeloma) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Daratumumab (multiples Myelom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 November 2017). 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:

Daratumumab (multiple myeloma) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:

Federal Joint Committee

Commission awarded on:

15 August 2017

Internal Commission No.:

A17-40

Address of publisher:

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

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Keywords: daratumumab, multiple myeloma, benefit assessment, NCT02076009

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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
BSC	best supportive care
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30
EQ-5D	European Quality of Life-5 Dimensions
FDA	Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IMF	International Myeloma Foundation
IMiD	immunomodulatory drug
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ISS	International Staging System
PFS	progression-free survival
PI	proteasome inhibitor
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book 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 daratumumab. 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 15 August 2017.

Research question

The aim of the present report was to assess the added benefit of daratumumab as monotherapy, or in combination with lenalidomide and dexamethasone, or in combination with bortezomib and dexamethasone, in comparison with the appropriate comparator therapy (ACT) in adult patients with multiple myeloma.

In its specification of the ACT, the G-BA distinguished between 2 research questions, which are presented in Table 2.

Table 2: Research questions of the benefit assessment of daratumumab

Research question	Subindication	ACT[a]
1	Daratumumab in combination with lenalidomide and dexamethasone, or in combination with bortezomib and dexamethasone: adult patients with multiple myeloma who have received at least one prior therapy[b]	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
2	Daratumumab as monotherapy: adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a PI and an IMiD, and who have demonstrated disease progression on the last therapy[c]	Individual treatment specified by the physician under consideration of prior therapies, duration and extent of the response, and the approval of the drugs[d]

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: It is assumed for the present therapeutic indication that the use of daratumumab in combination with lenalidomide and dexamethasone, or in combination with bortezomib and dexamethasone, is conducted in the framework of a remission-inducing induction treatment. High-dose chemotherapy with stem cell transplantation, which may be a subsequent treatment option, is therefore not an option as part of the ACT.
c: It is assumed for the present therapeutic indication that high-dose chemotherapy with stem cell transplantation is not an option at the time point of their current treatment.
d: This also includes BSC, which ensures best possible supportive therapy, optimized for the individual patient, for alleviation of symptoms and improvement in the quality of life.
ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; IMiD: immunomodulatory drug; PI: proteasome inhibitor

For easier presentation and better readability, the report uses the following terms for the research questions:

- adults with multiple myeloma who have received at least one prior therapy (research question 1)
- adults with relapsed and refractory multiple myeloma (research question 2)

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

Results

Research question 1: adults with multiple myeloma who have received at least one prior therapy

Study pool and study characteristics

The 2 randomized controlled trials (RCTs) POLLUX and CASTOR were principally relevant for the benefit assessment. Both studies are ongoing, open-label studies in adults with multiple myeloma who have received at least one prior therapy and who have had documented progression after the last therapy.

Only the POLLUX study was included in the present benefit assessment. The analyses presented by the company on the total population of the CASTOR study were not used. This is justified below.

Study CASTOR

The CASTOR study compares the combination of daratumumab + bortezomib + dexamethasone with bortezomib + dexamethasone. A total of 498 patients were randomly assigned to the study arms: 251 patients to the daratumumab arm and 247 patients to the comparator arm. Treatment of the patients in both study arms was in compliance with the Summaries of Characteristics (SPCs) of daratumumab and bortezomib.

According to the SPC, bortezomib is approved for patients with multiple myeloma who have received at least one prior therapy and who have already undergone or are unsuitable for haematopoietic stem cell transplantation. Before the start of the CASTOR study, about 61% of the patients included had received autologous stem cell transplantation and were therefore candidates for treatment with bortezomib. For the remaining 39% of the patients included, it was not clear from the study documents whether and how many of these patients were actually unsuitable for stem cell transplantation.

Since it has not been clarified whether and how many patients without prior stem cell transplantation were actually unsuitable for this treatment, and since, in addition, the company did not address this problem at all in the dossier, the analyses presented by the company on the total population of the CASTOR study were not used for the present benefit assessment.

Assessment of the POLLUX study

The POLLUX study compares the combination of daratumumab + lenalidomide + dexamethasone with lenalidomide + dexamethasone. A total of 569 patients were randomly assigned to the study arms: 286 patients to the daratumumab arm and 283 patients to the comparator arm. Treatment in both study arms was in 28-day cycles, with daratumumab and lenalidomide being administered in compliance with the recommendations of the SPCs of daratumumab and lenalidomide. Dexamethasone, in contrast, was used in a lower dosage than recommended in the SPC of lenalidomide for the present therapeutic indication. The specific handling of this issue is described below.

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

Patients were treated until disease progression or occurrence of unacceptable toxicity.

Handling of the fact that dexamethasone was not used in compliance with the approval in the POLLUX study

A dexamethasone dosage deviating from the approval was used in the comparator arm of the POLLUX study. The adequacy of this deviating dosing regimen is at least questionable. The same situation occurred in a study (ELOQUENT-2) in the benefit assessment of elotuzumab in the same therapeutic indication because the same dosage regimen of dexamethasone deviating from the approval was also used in the comparator arm of this study. The G-BA used this study because it considered there to be "a medical reason in the specific treatment and health care situation in the present therapeutic indication, providing the exceptional justification to use the data from the ELOQUENT-2 study to allow a benefit assessment of elotuzumab". With reference to the G-BA's decision and justification on elotuzumab, the POLLUX study was included in the present benefit assessment in the present therapeutic indication despite the fact that the dosage of dexamethasone used in the comparator arm deviates from the approval.

Risk of bias at study level and outcome level

The risk of bias at study level for the POLLUX study was rated as low. The risk of bias at outcome level was rated as high for all outcomes except for the outcome "overall survival".

Results

Mortality: overall survival

A statistically significant difference in favour of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone was shown for the outcome "overall survival".

Moreover, there was an effect modification by the characteristic "sex" for this outcome. For women, there was an indication of an added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone. For men, there was no hint of an added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone; an added benefit is therefore not proven.

Morbidity: health status (EQ-5D VAS) and symptoms (EORTC QLQ-C30)

No statistically significant difference between the treatment groups was shown for the outcome "health status" (European Quality of Life-5 Dimensions visual analogue scale [EQ-5D VAS]) or for the following symptom (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 [EORTC QLQ-C30]) outcomes:

fatigue, nausea/vomiting, pain, dyspnoea, loss of appetite and constipation. Hence, there was no hint of an added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone for these outcomes; an added benefit is therefore not proven.

There were also no statistically significant differences between the treatment arms for the symptom outcomes "insomnia" and "diarrhoea", but there was an effect modification for both outcomes. There was proof of an effect modification by the characteristic "International Staging System (ISS) stage at the start of the study" for the outcome "insomnia". No statistically significant difference between the treatment arms was shown for patients with ISS stage I and III; there was no hint of an added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone; an added benefit is therefore not proven. For patients with ISS stage II, in contrast, a statistically significant difference was shown between the treatment arms; there was a hint of an added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone. There was an effect modification by the characteristic "ethnicity" for the outcome "diarrhoea". No statistically significant difference between the treatment arms was shown for patients of Asian and other origin; there was no hint of an added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone; an added benefit is therefore not proven. For Caucasians, in contrast, a statistically significant difference was shown between the treatment arms; there was a hint of an added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone.

Health-related quality of life: functional scales (EORTC QLQ-C30)

No statistically significant difference between the treatment groups was shown for each of the outcomes "general health status", "role functioning", "emotional functioning" and "cognitive functioning". Hence, there was no hint of an added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone for these outcomes; an added benefit is therefore not proven.

A statistically significant difference in favour of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone was shown for the outcome "social functioning". This resulted in a hint of an added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone.

There was no statistically significant difference between the treatment groups for the outcome "physical functioning". However, there was proof of an effect modification by the characteristic "age". No statistically significant difference between the treatment arms was shown for adults ≥ 65 years of age; there was no hint of an added benefit of daratumumab + lenalidomide + dexamethasone; an added benefit is therefore not proven. For adults < 65 years of age, in contrast, a statistically significant difference was shown between the

treatment arms; there was a hint of lesser benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone.

Side effects

There were no statistically significant differences between the treatment groups for the outcomes "serious adverse events (SAEs)" and "discontinuation due to AEs" (of all drug components). Hence, there was no hint of greater or lesser harm from daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone for any of these outcomes; greater or lesser harm is therefore not proven for these outcomes.

A statistically significant difference to the disadvantage of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone was shown for the outcome "severe AEs" (Common Terminology Criteria for Adverse Events [CTCAE] grade 3–4). Moreover, there was an effect modification by the characteristic "ISS stage at the start of the study" for this outcome. No statistically significant difference between the treatment arms was shown for patients with ISS stage II and III; there was no hint of an added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone; an added benefit is therefore not proven. For patients with ISS stage I, in contrast, a statistically significant difference was shown between the treatment arms; there was a hint of greater harm of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone.

A statistically significant difference to the disadvantage of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone was shown for the following specific AE outcomes: gastrointestinal disorders, respiratory, thoracic and mediastinal disorders, and febrile neutropenia. This resulted in a hint of greater harm of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone in each case.

Research question 2: adults with relapsed and refractory multiple myeloma

Concurring with the company, the check of the completeness of the study pool produced no RCTs on the comparison of daratumumab versus the ACT. For this reason, the company conducted an information retrieval for further investigations. Based on the search results, the company identified the single-arm study SIRIUS for daratumumab and the retrospective observational study International Myeloma Foundation (IMF) cohort for the ACT.

The SIRIUS study included patients with multiple myeloma who had received at least 3 prior therapies, including a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD), or who were refractory to both a PI and an IMiD. The company presented analyses of those patients (N = 106) who were receiving approval-compliant treatment with daratumumab over the total study period.

The IMF cohort included patients with relapsed multiple myeloma who had received at least 3 prior therapies and who were refractory to both a PI and an IMiD. A total of 543 patients were included in the IMF cohort. The results of the company were primarily based on analyses of the patients from Germany (N = 28). The company additionally presented the results of patients (N = 234) from Europe who were treated with substances approved in Germany. Results of the total IMF cohort are reported in the publication Kumar 2017.

Overall, the data presented by the company were unsuitable to draw conclusions on the added benefit of daratumumab in comparison with the ACT. The reasons were as follows:

- The main reason was that the company did not consider individual patients in its analyses of the IMF cohort, but the number of the lines of treatment. For instance, the 28 German patients were included in the analyses as 54 lines of treatment. For 28 patients of the IMF cohort from Germany, the analyses presented by the company resulted in 40 events for the outcome "overall survival". These analyses are inadequate and hence unsuitable for the benefit assessment. Analyses based on actually observed patients are required. These analyses were not available, however.
- The company did not provide reasons why it primarily used the results of patients from Germany and Europe, and not of the total IMF cohort for its analyses.
- The similarity of the study populations was questionable because information was not available for all characteristics.
- The comparison of the data from the SIRIUS study and of the total IMF cohort, a comparison of individual arms of different studies, overall showed no effects that were so large that they could not be caused by systematic bias alone.

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

On the basis of the results presented, the probability and the extent of the added benefit of the drug daratumumab compared with the ACT is assessed as follows:

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

Research question 1: adults with multiple myeloma who have already received one prior therapy

The overall assessment showed both positive and negative effects – partly also in subgroups – with differences in the certainty of results (indication or hints) for daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone.

The results showed an effect modification by sex for the outcome "overall survival". For women, this resulted in an indication of a major added benefit for this outcome. For men, the added benefit is not proven for this outcome. Under consideration of the positive and negative effects, the overall conclusion on the added benefit was therefore derived separately for women and men. In the overall consideration, positive effects outweigh negative effects for women, whereas for men, positive and negative effects are overall balanced. This is due to the fact that the hints of greater harm on the side of negative effects mostly have the extent "minor". The outcome "severe AEs" (CTCAE grade 3–4) in patients with ISS stage I is an exception as there is greater harm with the extent "major". However, since there was no information how the effects regarding this outcome are in men or women with this ISS stage I, this effect cannot be meaningfully interpreted in the balancing of positive and negative effects.

In summary, there is an indication of a major added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone for women with multiple myeloma who have received at least one prior therapy. For men with multiple myeloma who have received at least one prior therapy, there is, in summary, no hint of an added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone; the added benefit is therefore not proven.

Research question 2: adults with relapsed and refractory multiple myeloma

The data presented by the company for the assessment of the added benefit of daratumumab in adults with relapsed and refractory multiple myeloma, whose prior therapy included a PI and an IMiD, and who have demonstrated disease progression on the last therapy, were unsuitable to derive an added benefit. Hence an added benefit of daratumumab is not proven for these patients.

Table 3 presents a summary of the probability and extent of the added benefit of daratumumab.

Table 3: Daratumumab – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	Daratumumab in combination with lenalidomide and dexamethasone, or in combination with bortezomib and dexamethasone: adult patients with multiple myeloma who have received at least one prior therapy[b]	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	For daratumumab in combination with bortezomib and dexamethasone: ▪ added benefit not proven For daratumumab in combination with lenalidomide and dexamethasone: men: added benefit not proven women: indication of major added benefit
2	Daratumumab as monotherapy: adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a PI and an IMiD, and who have demonstrated disease progression on the last therapy[c]	Individual treatment specified by the physician under consideration of prior therapies, duration and extent of the response, and the approval of the drugs[d]	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: It is assumed for the present therapeutic indication that the use of daratumumab in combination with lenalidomide and dexamethasone, or in combination with bortezomib and dexamethasone, is conducted in the framework of a remission-inducing induction treatment. High-dose chemotherapy with stem cell transplantation, which may be a subsequent treatment option, is therefore not an option as part of the ACT.
c: It is assumed for the present therapeutic indication that high-dose chemotherapy with stem cell transplantation is not an option at the time point of their current treatment.
d: This also includes BSC, which ensures best possible supportive therapy, optimized for the individual patient, for alleviation of symptoms and improvement in the quality of life.
ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; IMiD: immunomodulatory drug; PI: proteasome inhibitor

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

Supplementary note

The result of the assessment deviates from the result of the G-BA assessment in the framework of the market access in 2016, where the G-BA had determined a non-quantifiable added benefit of daratumumab monotherapy. However, in this assessment, the added benefit had been regarded as proven by the approval because of the special situation for orphan drugs, irrespective of the underlying data.

2.2 Research question

The aim of the present report was to assess the added benefit of daratumumab as monotherapy, or in combination with lenalidomide and dexamethasone, or in combination with bortezomib and dexamethasone, in comparison with the ACT in adult patients with multiple myeloma.

In its specification of the ACT, the G-BA distinguished between 2 research questions, which are presented in Table 4.

Table 4: Research questions of the benefit assessment of daratumumab

Research question	**Subindication**	**ACT[a]**
1	Daratumumab in combination with lenalidomide and dexamethasone, or in combination with bortezomib and dexamethasone: adult patients with multiple myeloma who have received at least one prior therapy[b]	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
2	Daratumumab as monotherapy: adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a PI and an IMiD, and who have demonstrated disease progression on the last therapy[c]	Individual treatment specified by the physician under consideration of prior therapies, duration and extent of the response, and the approval of the drugs[d]

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: It is assumed for the present therapeutic indication that the use of daratumumab in combination with lenalidomide and dexamethasone, or in combination with bortezomib and dexamethasone, is conducted in the framework of a remission-inducing induction treatment. High-dose chemotherapy with stem cell transplantation, which may be a subsequent treatment option, is therefore not an option as part of the ACT.
c: It is assumed for the present therapeutic indication that high-dose chemotherapy with stem cell transplantation is not an option at the time point of their current treatment.
d: This also includes BSC, which ensures best possible supportive therapy, optimized for the individual patient, for alleviation of symptoms and improvement in the quality of life.
ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; IMiD: immunomodulatory drug; PI: proteasome inhibitor

For easier presentation and better readability, the report uses the following terms for the research questions:

- adults with multiple myeloma who have received at least one prior therapy (research question 1)

- adults with relapsed and refractory multiple myeloma (research question 2)

In its dossier, the company investigated research question 1 in Module 3 A and Module 4 A, and research question 2 in Module 3 B and in Module 4 B. The company followed the ACT specified by the G-BA (see Section 2.6.1 of the full dossier assessment).

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

2.3 Research question 1: adults with multiple myeloma who have received at least one prior therapy

2.3.1 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 daratumumab (status: 12 June 2017)
- bibliographical literature search on daratumumab (last search on 19 June 2017)
- search in trial registries for studies on daratumumab (last search on 12 June 2017)

To check the completeness of the study pool:

- search in trial registries for studies on daratumumab (last search on 23 August 2017)

The check identified no additional relevant study.

2.3.1.1 Studies included

The studies listed in the following table were relevant for the benefit assessment:

Table 5: Study pool – RCT, direct comparison

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
Daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone			
MMY3003 (POLLUX[b])	Yes	Yes	No
Daratumumab + bortezomib + dexamethasone vs. bortezomib + dexamethasone			
MMY3004 (CASTOR[b])	Yes	Yes	No

a: Study for which the company was sponsor.
b: Hereinafter, the study is referred to with this abbreviated form.
RCT: randomized controlled trial; vs.: versus

The POLLUX study compares a combination of daratumumab + lenalidomide + dexamethasone with lenalidomide + dexamethasone. The CASTOR study compares the combination of daratumumab + bortezomib + dexamethasone with bortezomib + dexamethasone. Both studies presented were generally relevant for the benefit assessment. Hence the study pool concurred with the one of the company.

The analyses presented by the company for the total population of the CASTOR study could not be used for the present benefit assessment. This is justified below.

Description of the CASTOR study

The CASTOR study [3] is an ongoing, open-label RCT on the comparison of daratumumab + bortezomib + dexamethasone with bortezomib + dexamethasone in adults with multiple myeloma who have received at least one prior therapy and who have had documented progression after the last therapy. In addition, patients had to be in a general condition corresponding to an Eastern Cooperative Oncology Group Performance Status [ECOG PS] of 0 to 2. Patients with refractoriness or intolerance to bortezomib were excluded. A total of 498 patients were randomly assigned to the study arms: 251 patients to the daratumumab arm and 247 patients to the comparator arm. Treatment of the patients in both study arms was in compliance with the SPCs of daratumumab [4] and bortezomib [5]. The primary outcome of the study was PFS. Relevant secondary outcomes were overall survival, symptoms, health-related quality of life and adverse events.

Tables on further characteristics of the CASTOR study can be found in Appendix A of the full dossier assessment.

Suitability of the total population of the CASTOR study for the benefit assessment unclear

According to the SPC, bortezomib is approved for patients with multiple myeloma who have received at least one prior therapy and who have already undergone or are unsuitable for haematopoietic stem cell transplantation [5]. Before the start of the CASTOR study, about 61% of the patients included had received autologous stem cell transplantation and were therefore candidates for treatment with bortezomib. For the remaining 39% of the patients included, it was not clear from the study documents whether and how many of these patients were actually unsuitable for stem cell transplantation.

- Prior stem cell transplantation or non-eligibility for it was no inclusion criterion of the CASTOR study. Patients with prior allogeneic stem cell transplantation were excluded from the study.
- The company did not provide reasons for the patients' non-eligibility for stem cell transplantation. Instead, the company did not address this problem at all in the dossier, although the limitation of the patient population regarding stem cell transplantation is clearly described in the SPC of bortezomib [5].

- The company did not present any subgroup analyses for the characteristic of prior stem cell transplantation in the dossier. It was therefore not possible to assess the subpopulation with prior stem cell transplantation, which is comprised by the approval of bortezomib.

Summary

Since it has not been clarified whether and how many patients without prior stem cell transplantation were actually unsuitable for this treatment, and since, in addition, the company did not address this problem at all in the dossier, the analyses presented by the company on the total population of the CASTOR study were not used for the present benefit assessment.

The data presented by the company for adults with multiple myeloma who have received at least one therapy therefore allowed no conclusions on the added benefit of daratumumab in combination with bortezomib and dexamethasone in comparison with the ACT. The POLLUX study was used for the assessment of the added benefit of daratumumab in combination with lenalidomide and dexamethasone in comparison with the ACT.

Section 2.3.4 contains a reference list for the included POLLUX study.

2.3.1.2 Study characteristics

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

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

Study	Study design	Population	Interventions (numbers of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
POLLUX	RCT, open-label, parallel	Adults (≥ 18 years) with multiple myeloma who have received at least one prior therapy[b] and who have had documented progression after the last therapy; ECOG PS ≤ 2	Daratumumab + lenalidomide + dexamethasone (N = 286) lenalidomide + dexamethasone (N = 283)	▪ Screening: ≤ 21 days before the first cycle ▪ Treatment: until disease progression or occurrence of unacceptable toxicity ▪ Observation: outcome-specific, at most until death, end of study, or withdrawal of consent	136 centres in Australia, Belgium, Canada, Denmark, France, Germany, Greece, Israel, Japan, Korea, Netherlands, Poland, Russia, Spain, Sweden, Taiwan, United Kingdom, USA 6/2014–ongoing first data cut-off: 7 March 2016 second data cut-off: 30 June 2016	Primary: PFS Secondary: overall survival, morbidity, health-related quality of life, AEs

a: Primary outcomes include information without consideration of its relevance for this benefit assessment. Secondary outcomes exclusively include information on the relevant available outcomes for this benefit assessment.
b: Non-permitted prior therapies: daratumumab or other anti-CD38 therapies, allogeneic stem cell transplantation, ASCT within 12 weeks before randomization. Patients with intolerance or refractoriness to lenalidomide were excluded from the study.

AE: adverse event; ASCT: autologous stem cell transplantation; 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 intervention – RCT, direct comparison: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone

Study	Intervention	Comparison
POLLUX	Daratumumab 16 mg/kg BW IV: ▪ cycle 1–2, weekly: day 1, 8, 15 and 22 ▪ cycle 3–6, every 2 weeks: day 1 and 15 ▪ from cycle 7, every 4 weeks: day 1 + lenalidomide from cycle 1, day 1–21 ▪ 25 mg orally if creatinine clearance > 60 mL/min ▪ 10 mg orally if creatinine clearance 30–60 mL/min + dexamethasone 40 mg/week[a] (≤ 75 years) or 20 mg/week (> 75 years or BMI < 18.5) orally from cycle 1 1 cycle is 4 weeks	Lenalidomide from cycle 1, day 1–21 ▪ 25 mg orally if creatinine clearance > 60 mL/min ▪ 10 mg orally if creatinine clearance 30–60 mL/min + dexamethasone 40 mg/week (≤ 75 years) or 20 mg/week (> 75 years or BMI < 18.5) orally from cycle 1 1 cycle is 4 weeks
	Treatment adjustments ▪ dose adjustments for daratumumab not allowed[b] ▪ dose adjustments for lenalidomide in accordance with the SPC allowed ▪ dose reduction or discontinuation for dexamethasone allowed in case of AEs	
	Pretreatment and concomitant treatment	
	Premedication before daratumumab ▪ paracetamol (acetaminophen) 650 to 1000 mg IV or orally ▪ antihistamine (diphenhydramine 25–50 mg or equivalent) ▪ leukotriene inhibitors (optional at cycle 1, day 1): montelukast 10 mg orally or equivalent The oral premedication can be taken at home if administered 1 to 3 hours before the daratumumab infusion. **Postmedication after daratumumab** Patients with a higher risk of respiratory complications[c] may receive control medication for lung disease: ▪ antihistamine (diphenhydramine or equivalent) on day 1 and 2 after all infusions ▪ short-acting beta 2-adrenergic receptor agonist (e.g. salbutamol) ▪ inhaled corticosteroids ± long-acting beta 2 adrenergic receptor agonists for asthma ± long-acting bronchodilators such as tiotropium or salmeterol for COPD	

(continued)

Table 7: Characteristics of the intervention – RCT, direct comparison: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone (continued)

Study	Intervention	Comparison
POLLUX	**Pretreatment and concomitant treatment**	
	Concomitant treatment ▪ concomitant medication for the treatment of infusion-related reactions ▪ growth factors (e.g. CSF), platelet or erythrocyte transfusions ▪ antiinfective agents (e.g. for the treatment of *Pneumocystitis carinii* and herpes zoster) ▪ antihistamine ▪ bisphosphonates for patients with myeloma-related bone disorder ▪ acetylsalicylic acid or low molecular weight heparin (for the prophylaxis of deep vein thrombosis or pulmonary embolism) ▪ radiotherapy ▪ antiarrhythmics and other supportive cardiac drugs, antiepileptics ▪ treatment for the prophylaxis of tumour lysis syndrome **Non-permitted concomitant treatment** ▪ other antineoplastic myeloma therapies ▪ other systemic corticosteroids (> 10 mg prednisone/day or equivalent) and NSAID should be avoided	

a: On the day of the administration of daratumumab, half of the dexamethasone dose was administered IV or orally 1–3 hours before the daratumumab infusion; the other half was taken orally on the next day.
b: In case of IRR, and depending on the severity, the infusion is interrupted until stabilization, the infusion speed is adjusted or treatment is stopped.
c: E.g. COPD patients with FEV1 < 80% or with mild asthma.
BMI: body mass index; BW: body weight; COPD: chronic obstructive pulmonary disease; CSF: colony-stimulating factors; FEV1: forced expiratory volume in 1 second; IRR: infusion-related reaction; IV: intravenously; NSAID: nonsteroidal anti-inflammatory drug; RCT: randomized controlled trial; vs.: versus

Study design

The POLLUX study is a randomized, open-label, active-controlled approval study on the comparison of daratumumab + lenalidomide + dexamethasone with lenalidomide + dexamethasone alone. It is a multicentre study conducted in 136 study centres in 18 countries.

Adults with multiple myeloma with at least one prior therapy and documented progression after the last therapy were included in the study. In addition, patients had to be in a general condition corresponding to an ECOG PS of 0 to 2. Patients with refractoriness or intolerance to lenalidomide were excluded. Hence, the population investigated in the POLLUX study corresponded to the therapeutic indication of daratumumab in the present research question.

Randomization of the patients was stratified by ISS stage at screening (I, II or III), the number of prior lines of treatment (1 versus 2 or 3 versus > 3) and prior lenalidomide treatment (no versus yes). A total of 569 patients were randomly assigned to the study arms: 286 patients to the daratumumab arm and 283 patients to the comparator arm.

Treatment in both study arms was in 28-day cycles, with daratumumab and lenalidomide being administered in compliance with the recommendations of the SPCs of daratumumab

and lenalidomide [4,6]. Dexamethasone, in contrast, was used in a lower dosage than recommended in the SPC of lenalidomide for the present therapeutic indication [6]. The specific handling of this issue is described below.

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

Patients were treated until disease progression or occurrence of unacceptable toxicity. Patients whose daratumumab treatment was stopped could continue treatment with lenalidomide and dexamethasone, and patients whose treatment with lenalidomide and dexamethasone was stopped, could continue treatment with daratumumab.

Handling of the fact that dexamethasone was not used in compliance with the approval in the POLLUX study

The dosing regimen of dexamethasone used in the POLLUX study deviates from the recommendations in the SPC of lenalidomide [6], which describes the approved dosing regimen of the combination partner dexamethasone in the therapeutic indication of multiple myeloma. Table 8 compares the approval-compliant dosage of dexamethasone with the dosage given in the intervention and comparator arm of the POLLUX study.

Table 8: Comparison of the approval-compliant dexamethasone dosage with the dexamethasone dosage given in the POLLUX study

Dexamethasone dosage	**Cycle[a] 1–4**			**From cycle[a] 5**		
According to the approval [6][b]	**Cycle day**					
	1–4	**9–12**	**17–20**	**1–4**	**9–12**	**17–20**
Daily dose (mg)	40	40	40	40	–	–
Total dose per cycle[a] (mg)	480 (pulse administration)			160 (pulse administration)		
Study POLLUX (intervention and comparator arm)	**Cycle day**					
	1	**8**	**15**	**22**	**1**	**8**	**15**	**22**
Daily dose (mg)	40	40	40	40	40	40	40	40
Total dose per cycle[a] (mg)	160 (non-pulse administration)				160 (non-pulse administration)			

a: 28-day cycle.
b: In combination with daratumumab + lenalidomide or lenalidomide in patients with multiple myeloma with at least one prior therapy.
–: no dexamethasone given

Hence the dosage regimen of dexamethasone used in the POLLUX study deviates from the dosing regimen described in the SPC of lenalidomide [6] both in the dose per cycle and due to the missing pulse administration. Regarding the dosage of the combination partners lenalidomide and dexamethasone, the SPC of daratumumab refers to the dosing regimen used in the POLLUX study (Section 5.1 of the SPC), but also to the SPCs of the drugs used together with daratumumab, including the SPC of lenalidomide. Hence at least in the

comparator arm of the POLLUX study, the dosing regimen of dexamethasone does not comply with the approval because the SPC of lenalidomide is decisive for this arm.

From the company's point of view, the dosage of dexamethasone used in the POLLUX study in combination with lenalidomide concurs with German everyday health care. For this statement, the company referred to the G-BA decision on elotuzumab [7] in the same therapeutic indication and to statements by treating physicians and representatives of medical societies in the oral hearings on pomalidomide [8] and carfilzomib [9]. In addition, the company based its arguments on international [10] and national [11,12] guidelines for the treatment of multiple myeloma and on several studies [13-15].

It cannot be inferred from the guidelines and studies cited by the company that a lower dosage of dexamethasone is generally to be used in pretreated multiple myeloma. A detailed discussion of the guidelines and studies put forward by the company can be found in the dossier assessment on elotuzumab [16]. For this reason, it is at least questionable to what extent the dosing regimen of dexamethasone used in the POLLUX study is adequate.

The same situation as in the POLLUX study occurred in the ELOQUENT-2 study submitted for the benefit assessment of elotuzumab. The dexamethasone dosing regimen deviating from the approval, which is described in Table 8, was also used in the comparator arm of this study. Nonetheless, the G-BA used the study for the benefit assessment. In the justification [17] on the decision, the G-BA explained that the dexamethasone dosage prescribed in the SPC on lenalidomide was no longer used regularly in German everyday health care. Against this background, the G-BA considered there to be "a medical reason in the specific treatment and health care situation in the present therapeutic indication, providing the exceptional justification to use the data from the ELOQUENT-2 study to allow a benefit assessment of elotuzumab" [17]. At the same time, the G-BA noted that, "insofar as the dexamethasone dosage used in this study as a comparison was not used in compliance with the SPC, [...] no conclusions could be derived regarding the appropriateness in this therapeutic indication" [17].

This had the consequence for the present benefit assessment that, with reference to the G-BA's decision and justification, the POLLUX study was considered in the present benefit assessment despite the fact that the dosage of dexamethasone deviates from the approval.

Analysis and data cut-offs

Several analyses are planned in the POLLUX study. An interim analysis was conducted after about 80 patients had been treated for at least 8 weeks or had stopped their study treatment. Another interim analysis (first data cut-off from 7 March 2016) was conducted when 177 events of the primary outcome "PFS" were reached. Another analysis, which had not been prespecified by the company, was conducted in the framework of the 120-day safety update from 30 June 2016 required by the Food and Drug Administration (FDA) (second data cut-off) for the outcomes "PFS", "overall survival" and "safety". The POLLUX study is still

ongoing. The amendment to the study protocol from 26 May 2016 mandated another interim analysis on reaching 165 events of the outcome "overall survival". Section 2.3.2.1 describes for which data cut-off and for which outcomes data were available.

Planned duration of follow-up

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

Table 9: Planned duration of follow-up – RCT, direct comparison: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone

Study **Outcome category** **Outcome**	**Planned follow-up**
POLLUX	
Mortality	
Overall survival	Every 3 months until death
Morbidity	
Symptoms/health status	EORTC QLQ-C30 (symptom scales)/EQ-5D VAS: up to 16 weeks after discontinuation of treatment or progression, start of a new antitumour treatment, or death
Health-related quality of life	EORTC QLQ-C30 (functional scales): week 4, 8 and 16 after discontinuation of treatment or until progression, start of a new antitumour treatment, or death
Side effects	
All outcomes in the category "side effects"	Up to 30 days after the last dose of the study medication or start of a new antitumour treatment

AE: adverse event; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life-5 Dimensions; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus

For the outcome "overall survival", follow-up observation is planned until death. The observation periods for the outcomes "morbidity", "health-related quality of life" and "side effects" were systematically shortened because they were only recorded for the period of treatment with the study medication (plus 16 weeks for morbidity and health-related quality of life, and 30 days for side effects) or until the start of a new antitumour treatment (or until progression). 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.

Characteristics of the study population

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

Table 10: Characteristics of the study populations – RCT, direct comparison: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone

Study Characteristics Category	**Daratumumab + lenalidomide + dexamethasone**	**Lenalidomide + dexamethasone**
POLLUX	N[a] = 286	N[a] = 283
Age [years], mean (SD)	64 (9)	64 (9)
Sex [F/M], %	40/60	42/58
Ethnicity, n (%)		
Caucasian	207 (72.4)	186 (65.7)
Black/African American	5 (1.7)	11 (3.9)
Asian	54 (18.9)	46 (16.3)
Other[b]	20 (7.0)[c]	40 (14.1)[c]
ECOG PS, n (%)		
0	139 (48.6)	150 (53.0)
1	136 (47.6)	118 (41.7)
2	11 (3.8)	15 (5.3)
Myeloma type, n (%)		
IgG	164 (57.3)	167 (59.0)
IgA	55 (19.2)	56 (19.8)
IgM	2 (0.7)	0 (0)
IgD	5 (1.7)	6 (2.1)
IgE	0 (0)	0 (0)
FLC	55 (19.2)	46 (16.3)
FLC kappa	34 (11.9)	32 (11.3)
FLC lambda	21 (7.3)	14 (4.9)
Biclonal	1 (0.3)	0 (0)
Negative immune fixation	4 (1.4)	8 (2.8)
ISS[d], n (%)		
I	137 (47.9)	140 (49.5)
II	93 (32.5)	86 (30.4)
III	56 (19.6)	57 (20.1)
Disease duration: time from first diagnosis of the multiple myeloma until randomization [years], mean (SD)	4.6 (3.6)	4.8 (3.6)

(continued)

Table 10: Characteristics of the study populations – RCT, direct comparison: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone (continued)

Study Characteristics Category	Daratumumab + lenalidomide + dexamethasone	Lenalidomide + dexamethasone
POLLUX	N[a] = 286	N[a] = 283
Prior therapies, n (%)	286 (100.0)	283 (100.0)
Prior systemic treatment	286 (100.0)	283 (100.0)
Prior ASCT	180 (62.9)	180 (63.6)
Prior radiotherapy	65 (22.7)	57 (20.1)
Number of prior therapies, n (%)		
1	149 (52.1)	146 (51.6)
2	85 (29.7)	80 (28.3)
3	38 (13.3)	38 (13.4)
> 3	14 (4.9)	19 (6.7)
Prior PI, n (%)	245 (85.7)	242 (85.5)
Bortezomib	241 (84.3)	238 (84.1)
Carfilzomib	6 (2.1)	6 (2.1)
Ixazomib	2 (0.7)	2 (0.7)
Prior IMiD, n (%)	158 (55.2)	156 (55.1)
Lenalidomide	50 (17.5)	50 (17.7)
Pomalidomide	2 (0.7)	0 (0)
Thalidomide	122 (42.7)	125 (44.2)
Treatment discontinuation, n (%)[e, f]	66 (23.3)	132 (47.0)
Study discontinuation, n (%)[e]	34 (11.9)	55 (19.4)

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: "Other" comprises the following groups; American Indian or native Alaskan, Hawaiian or pacific, other, unknown, and not reported.
c: Institute's calculation.
d: ISS is based on the levels of serum beta 2 microglobulin and albumin.
e: Values refer to the first data cut-off (7 March 2016); data on the second data cut-off (30 June 2016) are not available.
f: Unclear whether the values refer to the discontinuation of all or of any of the treatment components.
ASCT: autologous stem cell transplantation; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; FLC: free light chains; IgA: immunoglobulin A; IgD: immunoglobulin D; IgE: immunoglobulin E; IgG: immunoglobulin G; IgM: immunoglobulin M; IMiD: immunomodulatory drug; ISS: International Staging System; M: male; n: number of patients in the category; N: number of randomized patients; PI: proteasome inhibitor; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The patient characteristics were largely comparable between the treatment groups of the POLLUX study. Most patients were white; the mean age was 64 years. The proportion of men (about 60%) was somewhat higher in both study arms than the proportion of women (about 40%). According to the inclusion criteria, all patients had received at least one systemic treatment for multiple myeloma before study inclusion. About half of the patients were

pretreated with 2 or more therapies. The majority of the patients included were allocated to ISS stage I or II and had an ECOG PS of 0 or 1.

There were notable differences between the study arms in treatment discontinuation, however. At the time point of the first data cut-off, 66 (23.3%) patients in the daratumumab arm and 132 (47.0%) patients in the comparator arm had discontinued the study treatment. The treatment discontinuations in both arms were largely due to disease progression (14.0% of the patients in the daratumumab arm and 33.9% in the comparator arm). Data on treatment and study discontinuation were only available for the first data cut-off, however, and it was unclear whether the information referred to the discontinuation of all or of any of the treatment components (see Section 2.6.2.4.2 of the full dossier assessment).

Course of the study

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

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

Study **Duration of the study phase** **Outcome category**	**Daratumumab + lenalidomide + dexamethasone**	**Lenalidomide + dexamethasone**
POLLUX	N = 286	N = 283
Treatment duration [months]		
First data cut-off: 7 March 2016		
Median [min; max]	13.14 [0.00; 20.70]	12.22 [0.00; 20.14]
Mean (SD)[a]	12.31 (4.26)	10.59 (4.92)
Second data cut-off: 30 June 2016		
Median [min; max]	16.61 [0.00; 24.41]	14.65 [0.00; 23.95]
Mean (SD)	ND	ND
Observation period [months][a]		
Overall survival		
First data cut-off: 7 March 2016		
Median [95% CI]	13.60 [13.31; 14.06]	13.54 [13.27; 14.00]
Mean (SD)	13.24 (3.49)	12.74 (3.96)
Second data cut-off: 30 June 2016		
Median [95% CI]	17.28 [17.02; 17.84]	17.28 [17.02; 17.84]
Mean (SD)	ND	ND
Morbidity, health-related quality of life, side effects	ND	ND

a: Referring to the safety population (283 vs. 281 patients).

CI: confidence interval; max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The differences in median treatment duration shown at the first data cut-off from 7 March 2016 (13.14 versus 12.22 months) increased until the second data cut-off from 30 June 2016 and were 16.61 months in the daratumumab arm versus 14.65 months in the comparator arm. The difference is due to different rates in treatment discontinuation.

The median observation period for the outcome "overall survival" in the study arms was about the same at both data cut-offs. No information on the observation period was available for the outcomes of the categories "morbidity", "health-related quality of life" and "side effects".

Risk of bias at study level

Table 12 shows the risk of bias at study level.

Table 12: Risk of bias at study level – RCT, direct comparison: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
POLLUX	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level for the POLLUX study was rated as low. This corresponds to the company's assessment.

Limitations resulting from the open-label study design are described in Section 2.3.2.2 with the outcome-specific risk of bias.

2.3.2 Results on added benefit

2.3.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.6.2.4.3 of the full dossier assessment):

- Mortality
  - Overall survival
- Morbidity
  - symptoms measured with the EORTC QLQ-C30 symptom scales

- health status measured 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
  - serious adverse events (SAEs)
  - discontinuation due to AEs
  - severe AEs (CTCAE grade 3–4)
  - febrile neutropenia (Preferred Term [PT]; SAE)
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.6.2.4.3 of the full dossier assessment).

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

Table 13: Matrix of outcomes – RCT, direct comparison: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone

Study	**Outcomes**									
Time point	**Overall survival**	**Health status (EQ-5D VAS)**	**Symptoms (EORTC QLQ-C30 symptom scales)**	**Health-related quality of life (EORTC QLQ-C30 functional scales)**	**SAEs**	**Discontinuation due to AEs**	**Severe AEs (CTCAE grade 3–4)**	**Gastrointestinal disorders**	**Respiratory, thoracic and mediastinal disorders**	**Febrile neutropenia (SAE)**
POLLUX										
First data cut-off (7 March 2016)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Second data cut-off (30 June 2016)	Y	No	No	No	Y	Y[a]	Y	No	No	Y

a: Data are available for discontinuation of all drug components, but not for discontinuation of any of the drug components.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; EQ-5D: European Quality of Life-5 Dimensions; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus; Y: yes

The data available for the outcomes included were from different data cut-offs. The company presented results of the first data cut-off (7 March 2016) for the outcomes on symptoms, health status and health-related quality of life, and results from the second data cut-off (30 June 2016) for overall survival and side effects. For specific AEs, however, only results on PTs, but not on System Organ Classes (SOCs) were available for the second data cut-off. Hence for these outcomes, the first data cut-off was used for the assessment, which is adequate in view of the short interval between the data cut-offs.

2.3.2.2 Risk of bias

Table 14 describes the risk of bias for the relevant outcomes.

Table 14: Risk of bias at study and outcome level – RCT, direct comparison: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone

Study		Outcomes									
	Study level	Overall survival	Health status (EQ-5D VAS)	Symptoms (EORTC QLQ-C30 symptom scales)	Health-related quality of life (EORTC QLQ-C30 functional scales)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade 3–4)	Gastrointestinal disorders	Respiratory, thoracic and mediastinal disorders	Febrile neutropenia (SAE)
POLLUX	L	L	H[a]	H[a]	H[a]	H[b]	H[a, b]	H[b]	H[b]	H[b]	H[b]

a: Lack of blinding in subjective recording of outcomes; in addition, except for discontinuation due to AEs: notable differences in response to the questionnaires in potentially informative censoring.
b: Potentially informative censoring (treatment discontinuation due to progression at the first data cut-off: 14% [daratumumab + lenalidomide + dexamethasone and 34% [control]) in conjunction with median treatment durations of 16.61 months (daratumumab + lenalidomide + dexamethasone) and 14.65 months (control) at the second data cut-off.
c: No usable data available.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life-5 Dimensions; H: high; L: low; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

The risk of bias for the outcome “overall survival” was rated as low. This concurs with the company’s assessment.

The risk of bias was rated as high for the outcomes on health status (EQ-5D VAS), on symptoms and on health-related quality of life (EORTC QLQ-C30) due to a lack of blinding in subjective recording of outcomes and notable differences in response to the questionnaires

between the arms. The company also rated the risk of bias as high for these outcomes (see Section 2.6.2.4.2 of the full dossier assessment).

The risk of bias for the outcomes “SAEs”, “discontinuation due to AES”, “severe AEs” CTCAE grade 3–4 and “specific AEs” was also rated as high due to potentially informative censoring. For the outcome “discontinuation due to AEs”, there was additionally the lack of blinding. The company also rated the risk of bias for all outcomes on side effects as high (see also Section 2.6.2.4.2 of the full dossier assessment for further explanations on the risk of bias).

2.3.2.3 Results

Table 15 summarizes the results for the comparison of daratumumab + lenalidomide + dexamethasone with lenalidomide + dexamethasone in adults with multiple myeloma who have received at least one prior therapy. Where necessary, the data from the company’s dossier were supplemented with the Institute’s calculations. Kaplan-Meier curves on overall survival and on the side effect outcomes can be found in Appendix B of the full dossier assessment. Results on common AEs are presented in Appendix C of the full dossier assessment.

Table 15: Results (time to event) – RCT, direct comparison: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone

Study **Outcome category** **Outcome**	**Daratumumab + lenalidomide + dexamethasone**		**Lenalidomide + dexamethasone**		**Daratumumab + lenalidomide + dexamethasone vs. lenalidomide + 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**
POLLUX					
Mortality (second data cut-off: 30 June 2016)					
Overall survival	286	NA 40 (14.0)	283	NA 56 (19.8)	0.63[a] [0.42; 0.95]; 0.027[b]
Morbidity (first data cut-off: 7 March 2016)					
Health status (EQ-5D VAS)[c]					
Deterioration ≥ 7 points	286	3.8 [ND] 170 (59.4)	283	3.7 [ND] 166 (58.7)	0.97[a] [0.78; 1.21]; 0.780
Deterioration ≥ 10 points	286	4.9 [ND] 152 (53.1)	283	4.7 [ND] 149 (52.7)	0.97[a] [0.77; 1.21]; 0.759
Improvement ≥ 7 points	286	5.6 [ND] 154 (53.8)	283	5.7 [ND] 135 (47.7)	1.14[a] [0.90; 1.44]; 0.280
Improvement ≥ 10 points	286	6.9 [ND] 140 (49.0)	283	9.3 [ND] 119 (42.0)	1.16[a] [0.90; 1.49]; 0.245
Symptoms (EORTC QLQ-C30, deterioration ≥ 10 points)[c]					
Fatigue	286	1.9 [ND] 186 (65.0)	283	2.0 [ND] 181 (64.0)	1.11[a] [0.90; 1.36]; 0.341
Nausea/vomiting	286	13.9 [ND] 117 (40.9)	283	10.3 [ND] 121 (42.8)	0.86[a] [0.66; 1.11]; 0.249
Pain	286	5.6 [ND] 143 (50.0)	283	5.6 [ND] 159 (56.2)	0.89[a] [0.70; 1.11]; 0.298
Dyspnoea	286	5.5 [ND] 152 (53.1)	283	5.7 [ND] 147 (51.9)	1.06[a] [0.84; 1.34]; 0.607
Insomnia	286	6.6 [ND] 144 (50.3)	283	3.7 [ND] 157 (55.5)	0.80[a] [0.63; 1.00]; 0.052
Appetite loss	286	7.2 [ND] 141 (49.3)	283	10.2 [ND] 128 (45.2)	1.08[a] [0.85; 1.38]; 0.536
Constipation	286	4.7 [ND] 145 (50.7)	283	3.3 [ND] 157 (55.5)	0.87[a] [0.69; 1.10]; 0.242
Diarrhoea	286	5.6 [ND] 159 (55.6)	283	5.7 [ND] 152 (53.7)	1.00[a] [0.79; 1.25]; 0.968

(continued)

Table 15: Results (time to event) – RCT, direct comparison: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone (continued)

Study Outcome category Outcome	Daratumumab + lenalidomide + dexamethasone		Lenalidomide + dexamethasone		Daratumumab + lenalidomide + dexamethasone vs. lenalidomide + 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
POLLUX					
Morbidity (first data cut-off: 7 March 2016)					
Symptoms (EORTC QLQ-C30, improvement ≥ 10 points)[c]					
Fatigue	286	4.7 [ND] 157 (54.9)	283	3.7 [ND] 161 (56.9)	0.88[a] [0.70; 1.10]; 0.253
Nausea/vomiting	286	NA 46 (16.1)	283	NA 40 (14.1)	1.12[a] [0.73; 1.71]; 0.614
Pain	286	3.7 [ND] 148 (51.7)	283	4.7 [ND] 141 (49.8)	1.11[a] [0.88; 1.41]; 0.369
Dyspnoea	286	NA 90 (31.5)	283	NA 80 (28.3)	1.12[a] [0.82; 1.52]; 0.472
Insomnia	286	NA 101 (35.3)	283	NA 106 (37.5)	0.87[a] [0.66; 1.15]; 0.327
Appetite loss	286	NA 63 (22.0)	283	NA 68 (24.0)	0.89[a] [0.63; 1.27]; 0.528
Constipation	286	NA 76 (26.6)	283	NA 58 (20.5)	1.30[a] [0.92; 1.84]; 0.132
Diarrhoea	286	NA 48 (16.8)	283	NA 31 (11.0)	1.52[a] [0.96; 2.39]; 0.072
Health-related quality of life (first data cut-off: 7 March 2016)					
EORTC QLQ-C30 functional scales (deterioration ≥ 10 points)[c]					
General health status	286	4.7 [ND] 153 (53.5)	283	4.7 [ND] 155 (54.8)	0.96[a] [0.76; 1.20]; 0.701
Physical functioning	286	5.9 [ND] 147 (51.4)	283	7.5 [ND] 136 (48.1)	1.09[a] [0.86; 1.38]; 0.484
Role functioning	286	3.7 [ND] 171 (59.8)	283	3.1 [ND] 169 (59.7)	0.92[a] [0.74; 1.14]; 0.446
Emotional functioning	286	6.6 [ND] 136 (47.6)	283	7.8 [ND] 134 (47.3)	1.04[a] [0.82; 1.32]; 0.753
Social functioning	286	3.8 [ND] 161 (56.3)	283	2.9 [ND] 175 (61.8)	0.80[a] [0.64; 0.995]; 0.045

(continued)

Table 15: Results (time to event) – RCT, direct comparison: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone (continued)

Study Outcome category Outcome	Daratumumab + lenalidomide + dexamethasone		Lenalidomide + dexamethasone		Daratumumab + lenalidomide + dexamethasone vs. lenalidomide + 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
POLLUX					
Health-related quality of life (first data cut-off: 7 March 2016)					
EORTC QLQ-C30 functional scales (deterioration ≥ 10 points)[c]					
Cognitive functioning	286	4.9 [ND] 159 (55.6)	283	4.6 [ND] 162 (57.2)	0.93[a] [0.74; 1.16]; 0.505
EORTC QLQ-C30 functional scales (improvement ≥ 10 points)[c]					
General health status	286	6.6 [ND] 139 (48.6)	283	6.5 [ND] 133 (47.0)	1.04[a] [0.82; 1.33]; 0.727
Physical functioning	286	NA 109 (38.1)	283	NA 104 (36.7)	1.06[a] [0.80; 1.39]; 0.703
Role functioning	286	11.4 [ND] 119 (41.6)	283	11.7 [ND] 116 (41.0)	0.96[a] [0.74; 1.25]; 0.783
Emotional functioning	286	17.9 [ND] 113 (39.5)	283	17.1 [ND] 107 (37.8)	1.07[a] [0.82; 1.40]; 0.631
Social functioning	286	NA 109 (38.1)	283	17.1 [ND] 102 (36.0)	1.07[a] [0.81; 1.40]; 0.646
Cognitive functioning	286	14.1 118 (41.3)	283	NA 97 (34.3)	1.29[a] [0.98; 1.69]; 0.071
Side effects (second data cut-off 30 June 2016)					
AEs	283	– 279 (98.6)	281	– 274 (97.5)	–
SAEs	283	14.3 [ND] 153 (54.1)	281	16.8 [ND] 126 (44.8)	1.14[d] [0.90; 1.44]; 0.290
Discontinuation due to AEs (of all drug components)	283	NA 24 (8.5)	281	NA 24 (8.5)	RR: 0.99 [0.58; 1.71]; > 0.999[e]
Discontinuation due to AEs (of any drug component)	No data available				
Severe AEs (CTCAE grade 3–4)	283	1.0 [ND] 235 (83.0)	281	3.4 [ND] 210 (74.7)	1.39 [1.15; 1.68]; < 0.001

(continued)

Table 15: Results (time to event) – RCT, direct comparison: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone (continued)

Study Outcome category Outcome	Daratumumab + lenalidomide + dexamethasone		Lenalidomide + dexamethasone		Daratumumab + lenalidomide + dexamethasone vs. lenalidomide + 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
POLLUX					
Specific AEs (first data cut-off 7 March 2016)[c]					
Gastrointestinal disorders	283	ND 216 (76.3)	281	ND 164 (58.4)	RR: 1.31 [1.16; 1.47]; < 0.001[f]
Respiratory, thoracic and mediastinal disorders	283	ND 170 (60.1)	281	ND 114 (40.6)	RR: 1.48 [1.25; 1.76]; < 0.001[f]
Febrile neutropenia	283	ND 12 (4.2)	281	ND 4 (1.4)	RR: 2.98 [0.97; 9.12]; 0.048[g]

a: Hazard ratio (including 95% CI) calculated using Cox proportional hazards model with treatment as sole explanatory variable and stratified by the factors ISS (I, II or III), number of prior therapies (1 vs. 2 or 3 vs. > 3) and prior therapy with lenalidomide (no vs. yes).
b: p-value calculated using log-rank test stratified by the factors ISS (I, II or III), number of prior therapies (1 vs. 2 or 3 vs. > 3) and prior therapy with lenalidomide (no vs. yes).
c: Data presented for the first data cut-off; no data are available for the second data cut-off.
d: Hazard ratio (including 95% CI and p-value) calculated using Cox proportional hazards model without consideration of the stratification factors.
e: Institute‘s calculation, unconditional exact test (CSZ method according to [18]).
f: Institute’s calculation of effect RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [18]).
g: Institute’s calculation, asymptotic. Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.

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 Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; ISS: International Staging System; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Based on the available data, at most indications, e.g. of an added benefit, can be derived for the outcome “overall survival”, and at most hints for the outcomes for all other outcomes due to the high risk of bias.

Hereinafter, the information on the assessment of the company always refer to the company’s summarizing assessment of the studies POLLUX and CASTOR. The present benefit assessment refers only to the results of the POLLUX study.

Mortality

Overall survival

A statistically significant difference in favour of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone was shown for the outcome "overall survival".

Moreover, there was an effect modification by the characteristic "sex" for this outcome. For women, there was an indication of an added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone. For men, there was no hint of an added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone; an added benefit is therefore not proven.

This deviates from the assessment of the company, which derived proof of an added benefit of daratumumab for the outcome "all-cause mortality" on the basis of the total population and did not consider the effect modification by sex.

Morbidity

Health status (EQ-5D VAS)

The outcome "health status" was recorded with the EQ-5D VAS. Both the time to improvement and the time to deterioration were considered. In each case, there was no statistically significant difference between the treatment groups. Overall, this resulted in no hint of an added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone for the outcome "health status"; an added benefit is therefore not proven.

This concurs with the company's assessment.

Symptoms (EORTC QLQ-C30)

Symptom outcomes were recorded using the symptom scales of the disease-specific instrument EORTC QLQ-C30. Both the time to deterioration and the time to improvement were considered.

Both analyses showed no statistically significant difference between the treatment groups for the following outcomes: fatigue, nausea/vomiting, pain, dyspnoea, appetite loss, and constipation. Hence, there was no hint of an added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone for these outcomes; an added benefit is therefore not proven.

Both analyses also showed no statistically significant differences between the treatment arms for the outcomes "insomnia" and "diarrhoea", but there was an effect modification for both outcomes. There was proof of an effect modification by the characteristic "ISS stage at the start of the study" for the analysis of the time to deterioration of the outcome "insomnia". For patients with ISS stage I and III, there was no hint of an added benefit of daratumumab +

lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone; an added benefit is therefore not proven. For patients with ISS stage II, in contrast, there was a hint of an added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone. There was an effect modification by the characteristic "ethnicity" for the analysis of the time to improvement of the outcome "diarrhoea". For patients of Asian and other origin, there was no hint of an added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone; an added benefit is therefore not proven. For Caucasians, in contrast, there was a hint of an added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone.

This deviates from the company's assessment, which derived no added benefit of daratumumab for symptoms on the basis of the total population and did not consider effect modifications.

Health-related quality of life

Health-related quality of life was recorded with the functional scales of the disease-specific instrument EORTC QLQ-C30 questionnaire. Both the time to deterioration and the time to improvement were considered. Both analyses showed no statistically significant difference between the treatment groups for each of the outcomes "general health status", "role functioning", "emotional functioning" and "cognitive functioning". Hence, there was no hint of an added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone for these outcomes; an added benefit is therefore not proven.

There was no statistically significant difference between the treatment groups for the analysis of the time to improvement for the outcome "social functioning". A statistically significant difference in favour of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone was shown for the time to deterioration of the outcome "social functioning". This resulted in a hint of an added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone.

For both analyses, there was no statistically significant difference between the treatment groups for the outcome "physical functioning". There was proof of an effect modification by the characteristic "age" for the analysis of the time to deterioration, however. For adults ≥ 65 years of age, there was no hint of an added benefit of daratumumab + lenalidomide + dexamethasone; an added benefit is therefore not proven. For adults < 65 years of age, in contrast, there was a hint of a lesser benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone.

This corresponds to the company's assessment.

Side effects

Serious adverse events, discontinuation due to adverse events

There were no statistically significant differences between the treatment groups for the outcomes "SAEs" and "discontinuation due to AEs" (of all drug components). Hence, there was no hint of greater or lesser harm from daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone for any of these outcomes; greater or lesser harm is therefore not proven for these outcomes.

This corresponds to the company's assessment.

Severe adverse events (CTCAE grade 3–4)

A statistically significant difference to the disadvantage of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone was shown for the outcome "severe AEs" (CTCAE grade 3–4).

Moreover, there was an effect modification by the characteristic "ISS stage at the start of the study" for this outcome. For patients with ISS stage II and III, there was no hint of an added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone; an added benefit is therefore not proven. For patients with ISS stage I, in contrast, there was a hint of greater harm of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone.

This deviates from the company's assessment, which found no hint of greater harm and did not consider the effect modification.

Specific adverse events

A statistically significant difference to the disadvantage of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone was shown for the following outcomes: gastrointestinal disorders, respiratory, thoracic and mediastinal disorders, and febrile neutropenia. This resulted in a hint of greater harm of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone in each case.

This deviates from the assessment of the company, which did not use specific AEs for the derivation of the added benefit.

2.3.2.4 Subgroups and other effect modifiers

The following subgroup characteristics were considered to be relevant for the present benefit assessment (see also Section 2.6.2.4.3 of the full dossier assessment):

- sex (men/women)
- age (< 65/≥ 65 years)

- ethnicity (Caucasian/Asian/other)
- ISS stage (stage I/stage II/stage III)
- number of prior therapies

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 results of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone are summarized in Table 16.

Table 16: Subgroups (time to event) – RCT, direct comparison: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone

Study **Outcome category** **Outcome** **Characteristic** **Subgroup**	**Daratumumab + lenalidomide + dexamethasone**		**Lenalidomide + dexamethasone**		**Daratumumab + lenalidomide + dexamethasone vs. lenalidomide + 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**
POLLUX						
Mortality (second data cut-off 30 June 2016)						
Overall survival						
Sex						
Men	173	NA 31 (17.9)	164	NA 32 (19.5)	0.82 [0.50; 1.36]	0.449
Women	113	NA 9 (8.0)	119	NA 24 (20.2)	0.30 [0.14; 0.69]	0.003
Total					Interaction:	0.0440
Symptoms (first data cut-off 7 March 2016)						
EORTC QLQ-C30, improvement ≥ 10 points						
Diarrhoea						
Ethnicity						
Caucasian	207	NA 39 (18.8)	186	NA 17 (9.1)	2.14 [1.21; 3.78]	0.009
Asian	54	NA 6 (11.1)	46	NA 12 (26.1)	0.41 [0.15; 1.12]	0.082
Other	25	NA 3 (12.0)	51	NA 2 (3.9)	3.42 [0.56; 20.87]	0.183
Total					Interaction:	0.006
EORTC QLQ-C30, deterioration ≥ 10 points						
Insomnia						
ISS staging						
Stage I	137	5.0 [ND] 79 (57.7)	140	4.6 [ND] 81 (57.9)	0.95 [0.70; 1.30]	0.759
Stage II	93	11.2 [ND] 41 (44.1)	86	2.9 [ND] 56 (65.1)	0.53 [0.35; 0.795]	0.002
Stage III	56	8.5 [ND] 24 (42.9)	57	10.4 [ND] 20 (35.1)	1.17 [0.64; 2.14]	0.607
Total					Interaction:	0.027

(continued)

Table 16: Subgroups (time to event) – RCT, direct comparison: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone (continued)

Study Outcome category Outcome Characteristic Subgroup	Daratumumab + lenalidomide + dexamethasone		Lenalidomide + dexamethasone		Daratumumab + lenalidomide + dexamethasone vs. lenalidomide + 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
POLLUX						
Health-related quality of life (first data cut-off: 7 March 2016)						
EORTC QLQ-C30, deterioration ≥ 10 points						
Physical functioning						
Age						
< 65	133	4.7 [ND] 73 (54.9)	140	8.9 [ND] 58 (41.4)	1.51 [1.06; 2.13]	0.021
≥ 65	153	8.1 [ND] 74 (48.4)	143	5.7 [ND] 78 (54.5)	0.84 [0.61; 1.15]	0.271
Total					Interaction:	0.019
Side effects (second data cut-off 30 June 2016)						
Severe AEs (CTCAE grade 3 or 4)						
ISS staging						
Stage I	136	0.8 [ND] 113 (83.1)	139	7.1 [ND] 94 (67.6)	1.80 [1.37; 2.38]	< 0.001
Stage II	93	1.4 [ND] 73 (78.5)	86	2.3 [ND] 70 (81.4)	1.00 [0.72; 1.40]	> 0.999
Stage III	54	0.7 [ND] 49 (90.7)	56	1.2 [ND] 46 (82.1)	1.27 [0.84; 1.92]	0.251
Total					Interaction:	0.032

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HR: hazard ratio; ISS: International Staging System; n: number of patients with event; N: number of analysed patients; NA: not achieved; ND: no data; RCT: randomized controlled trial; vs.: versus

Mortality

Overall survival

There was an indication of an effect modification by the subgroup characteristic "sex" for the outcome "mortality". For men, there was no statistically significant difference between the treatment groups. Hence, there was no hint of an added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone for men; an added benefit for men is therefore not proven. For women, there was a statistically significant

difference in favour of daratumumab + lenalidomide + dexamethasone. This resulted in an indication of an added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone for women.

This deviates from the approach of the company, which did not consider effect modifications in the derivation of the added benefit.

Morbidity

Symptoms (EORTC QLQ-C30)

There was proof of an effect modification by the characteristic "ISS stage at the start of the study" for the outcome "insomnia" (time to deterioration). There was no statistically significant difference between the treatment arms for patients with ISS stage I and III. This resulted in no hint of an added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone; an added benefit is therefore not proven. A statistically significant difference in favour of daratumumab + lenalidomide + dexamethasone was shown for patients with ISS stage II. This resulted in a hint of an added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone.

There was proof of an effect modification by the characteristic "ethnicity" for the outcome "diarrhoea" (time to improvement). There was no statistically significant difference between the treatment arms for patients of Asian or other origin. This resulted in no hint of an added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone; an added benefit is therefore not proven. For Caucasians, in contrast, there was a statistically significant difference in favour of daratumumab + lenalidomide + dexamethasone. This resulted in a hint of an added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone.

This deviates from the approach of the company, which did not consider effect modifications in the derivation of the added benefit.

Health-related quality of life

There was proof of an effect modification by the characteristic "age" for the outcome "physical functioning" (time to deterioration). There was no statistically significant difference between the treatment arms for adults ≥ 65 years. This resulted in no hint of an added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone; an added benefit is therefore not proven. For adults < 65 years, in contrast, there was a statistically significant difference to the disadvantage of daratumumab + lenalidomide + dexamethasone. This resulted in a hint of lesser benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone.

This deviates from the approach of the company, which did not consider effect modifications in the derivation of the added benefit.

Side effects

Severe adverse events (CTCAE grade 3–4)

There was proof of an effect modification by the characteristic "ISS stage at the start of the study" for the outcome "severe AEs" (CTCAE grade 3–4). There was no statistically significant difference between the treatment arms for patients with ISS stage II and III. This resulted in no hint of an added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone; an added benefit is therefore not proven. For patients with ISS stage I, in contrast, there was a statistically significant difference to the disadvantage of daratumumab + lenalidomide + dexamethasone. This resulted in a hint of greater harm of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone.

This deviates from the approach of the company, which did not consider effect modifications in the derivation of the added benefit.

2.3.3 Probability and extent of added benefit

The derivation of probability and extent of the added benefit is presented below at outcome level, 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 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.

2.3.3.1 Assessment of added benefit at outcome level

The data presented in Section 2.3.2 resulted in the following assessments for daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone in adult patients with multiple myeloma who have received at least one prior therapy:

- an indication of an added benefit for the outcome "overall survival" for women
- a hint of an added benefit for the outcome "insomnia" for patients with ISS stage II at the start of the study
- a hint of an added benefit for the outcome "diarrhoea" for patients of Caucasian origin
- a hint of lesser benefit for the outcome "physical functioning" for adults < 65 years
- a hint of an added benefit for the outcome "social functioning"
- a hint of greater harm for each of the outcomes "gastrointestinal disorders", "respiratory, thoracic and mediastinal disorders" and "febrile neutropenia"
- a hint of greater harm for the outcome "severe AEs" (CTCAE grade 3–4) for patients with ISS stage I at the start of the study

Determination of the outcome category for the outcomes on symptoms (EORTC QLQ-C30) and on side effects

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

Since it could not be inferred from the dossier that the outcomes “insomnia” and “diarrhoea” (symptoms) of the EORTC QLQ-C30 were severe or serious symptoms, these outcomes were allocated to the outcome category of non-serious/non-severe symptoms/late complications. This allocation deviates from the assessment of the company insofar as the company did not allocate the outcomes presented to any outcome category.

The specific AE “febrile neutropenia” was allocated to the outcome category “serious/severe side effects” because it mainly referred to SAEs (febrile neutropenia). The specific AEs “respiratory, thoracic and mediastinal disorders” and “gastrointestinal disorders” were allocated to the outcome category “non-serious/non-severe symptoms/late complications” because, in comparison with common AEs, these were rated mostly as non-severe. This allocation deviates from the assessment of the company insofar as the company did not allocate the outcomes presented to any outcome category.

The extent of the respective added benefit at outcome level was estimated from these results (see Table 17).

Table 17: Extent of added benefit at outcome level: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone** **Median time to event or proportion of events** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality (second data cut-off 30 June 2016)		
Overall survival Sex		
Men	NA vs. NA HR: 0.82 [0.50; 1.36]; p = 0.449	Lesser benefit/added benefit not proven
Women	NA vs. NA HR: 0.30 [0.14; 0.69]; p = 0.003 probability: "indication"	Outcome category: mortality $CI_u < 0.85$ added benefit, extent: "major"
Morbidity (first data cut-off: 7 March 2016)		
Health status (EQ-5D VAS)		
Deterioration ≥ 7 points	3.8 vs. 3.7 months HR: 0.97 [0.78; 1.21]; p = 0.780	Lesser benefit/added benefit not proven
Deterioration ≥ 10 points	4.9 vs. 4.7 months HR: 0.97 [0.77; 1.21]; p = 0.759	
Improvement ≥ 7 points	5.6 vs. 5.7 months HR: 1.14 [0.90; 1.44]; p = 0.280	
Improvement ≥ 10 points	6.9 vs. 9.3 months HR: 1.16 [0.90; 1.49]; p = 0.245	
Symptoms (EORTC QLQ-C30, deterioration ≥ 10 points)		
Fatigue	1.9 vs. 2.0 months HR: 1.11 [0.90; 1.36]; p = 0.341	Lesser benefit/added benefit not proven
Nausea/vomiting	13.9 vs. 10.3 months HR: 0.86 [0.66; 1.11]; p = 0.249	Lesser benefit/added benefit not proven
Pain	5.6 vs. 5.6 months HR: 0.89 [0.70; 1.11]; p = 0.298	Lesser benefit/added benefit not proven
Dyspnoea	5.5 vs. 5.7 months HR: 1.06 [0.84; 1.34]; p = 0.607	Lesser benefit/added benefit not proven

(continued)

Table 17: Extent of added benefit at outcome level: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone** **Median time to event or proportion of events** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Morbidity (first data cut-off: 7 March 2016)		
Symptoms (EORTC QLQ-C30, deterioration ≥ 10 points)		
Insomnia		
ISS staging		
Stage I	5.0 vs. 4.6 months HR: 0.95 [0.70; 1.30]; p = 0.759	Lesser benefit/added benefit not proven
Stage II	11.2 vs. 2.9 months HR: 0.53 [0.35; 0.795]; p = 0.002 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: "considerable"
Stage III	8.5 vs. 10.4 months HR: 1.17 [0.64; 2.14]; p = 0.607	Lesser benefit/added benefit not proven
Appetite loss	7.2 vs. 10.2 months HR: 1.08 [0.85; 1.38]; p = 0.536	Lesser benefit/added benefit not proven
Constipation	4.7 vs. 3.3 months HR: 0.87 [0.69; 1.10]; p = 0.242	Lesser benefit/added benefit not proven
Diarrhoea	5.6 vs. 5.7 months HR: 1.00 [0.79; 1.25]; p = 0.968	Lesser benefit/added benefit not proven
Symptoms (EORTC QLQ-C30, improvement ≥ 10 points)		
Fatigue	4.7 vs. 3.7 months HR: 0.88 [0.70; 1.10]; p = 0.253	Lesser benefit/added benefit not proven
Nausea/vomiting	NA vs. NA HR: 1.12 [0.73; 1.71]; p = 0.614	Lesser benefit/added benefit not proven
Pain	3.7 vs. 4.7 months HR: 1.11 [0.88; 1.41]; p = 0.369	Lesser benefit/added benefit not proven
Dyspnoea	NA vs. NA HR: 1.12 [0.82; 1.52]; p = 0.472	Lesser benefit/added benefit not proven
Insomnia	NA vs. NA HR: 0.87 [0.66; 1.15]; p = 0.327	Lesser benefit/added benefit not proven
Appetite loss	NA vs. NA HR: 0.89 [0.63; 1.27]; p = 0.528	Lesser benefit/added benefit not proven
Constipation	NA vs. NA HR: 1.30 [0.92; 1.84]; p = 0.132	Lesser benefit/added benefit not proven

(continued)

Table 17: Extent of added benefit at outcome level: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone** **Median time to event or proportion of events** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Morbidity (first data cut-off: 7 March 2016)		
Symptoms (EORTC QLQ-C30, improvement ≥ 10 points)		
Diarrhoea Ethnicity		
Caucasian	NA vs. NA HR: 2.14 [1.21; 3.78]; p = 0.009 HR: 0.47 [0.26; 0.83][c] probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ added benefit, extent: "minor"
Asian	NA vs. NA HR: 0.41 [0.15; 1.12]; p = 0.082	Lesser benefit/added benefit not proven
Other	NA vs. NA HR: 3.42 [0.56; 20.87]; p = 0.183	Lesser benefit/added benefit not proven
Health-related quality of life (first data cut-off: 7 March 2016)		
EORTC QLQ-C30 functional scales (deterioration ≥ 10 points)		
General health status	4.7 vs. 4.7 HR: 0.96 [0.76; 1.20]; p = 0.701	Lesser benefit/added benefit not proven
Physical functioning Age		
< 65	4.7 vs. 8.9 months HR: 1.51 [1.06; 2.13]; p = 0.021 HR: 0.66 [0.47; 0.94][c] probability: "hint"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ lesser benefit, extent: "minor"
≥ 65	8.1 vs. 5.7 months HR: 0.84 [0.61; 1.15]; p = 0.271	Lesser benefit/added benefit not proven
Role functioning	3.7 vs. 3.1 months HR: 0.92 [0.74; 1.14]; p = 0.446	Lesser benefit/added benefit not proven
Emotional functioning	6.6 vs. 7.8 months HR: 1.04 [0.82; 1.32]; p = 0.753	Lesser benefit/added benefit not proven
Social functioning	3.8 vs. 2.9 months HR: 0.80 [0.64; 0.995]; p = 0.045 probability: "hint"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"
Cognitive functioning	4.9 vs. 4.6 months HR: 0.93 [0.74; 1.16]; p = 0.505	Lesser benefit/added benefit not proven

(continued)

Table 17: Extent of added benefit at outcome level: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone** **Median time to event or proportion of events** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Health-related quality of life (first data cut-off: 7 March 2016)		
EORTC QLQ-C30 functional scales (improvement ≥ 10 points)		
General health status	6.6 vs. 6.5 months HR: 1.04 [0.82; 1.33]; p = 0.727	Lesser benefit/added benefit not proven
Physical functioning	NA vs. NA HR: 1.06 [0.80; 1.39]; p = 0.703	Lesser benefit/added benefit not proven
Role functioning	11.4 vs. 11.7 months HR: 0.96 [0.74; 1.25]; p = 0.783	Lesser benefit/added benefit not proven
Emotional functioning	17.9 vs. 17.1 months HR: 1.07 [0.82; 1.40]; p = 0.631	Lesser benefit/added benefit not proven
Social functioning	NA vs. 17.1 months HR: 1.07 [0.81; 1.40]; p = 0.646	Lesser benefit/added benefit not proven
Cognitive functioning	14.1 months vs. NA HR: 1.29 [0.98; 1.69]; p = 0.071	Lesser benefit/added benefit not proven
Side effects		
SAEs	14.3 vs. 16.8 months HR: 1.14 [0.90; 1.44]; p = 0.290	Greater/lesser harm not proven
Discontinuation due to AEs (of all drug components)	8.5% vs. 8.5% RR: 0.99 [0.58; 1.71]; p < 0.999	Greater/lesser harm not proven
Discontinuation due to AEs (of any drug component)	No data available	Greater/lesser harm not proven
Severe AEs (CTCAE grade 3–4)		
ISS staging		
Stage I	0.8 vs. 7.1 months HR: 1.80 [1.37; 2.38]; p < 0.001 HR: 0.56 [0.42; 0.73][c] probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% greater harm, extent: "major"
Stage II	1.4 vs. 2.3 months HR: 1.00 [0.72; 1.40]; p > 0.999	Greater/lesser harm not proven
Stage III	0.7 vs. 1.2 months HR: 1.27 [0.84; 1.92]; p = 0.251	Greater/lesser harm not proven

(continued)

Table 17: Extent of added benefit at outcome level: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone** **Median time to event or proportion of events** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Gastrointestinal disorders	76.3% vs. 58.4% RR: 1.31 [1.16; 1.47]; p < 0.001 RR: 0.76 [0.68; 0.86][c] probability: "hint"	Outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ greater harm, extent: "minor"
Respiratory, thoracic and mediastinal disorders	60.1% vs. 40.6% RR: 1.48 [1.249; 1.76]; p < 0.001 RR: 0.68 [0.57; 0.801][c] probability: "hint"	Outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ greater harm, extent: "minor"
Febrile neutropenia	4.2% vs. 1.4% RR: 2.98 [0.97; 9.12]; p = 0.048 RR: 0.34 [0.11; 1.03][c] probability: "hint"	Outcome category: serious/severe side effects greater harm, extent: "minor"

a: Probability provided if a statistically significant and relevant effect is present.
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.

AE: adverse event; CI: confidence interval; CI_u: upper limit of 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 Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; ISS: International Staging System; NA: not achieved; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.3.3.2 Overall conclusion on added benefit

Table 18 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 18: Positive and negative effects from the assessment of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide and dexamethasone

Positive effects	**Negative effects**
Mortality ▪ Overall survival ▫ sex (women): indication of an added benefit – extent: “major”	
Health-related quality of life ▪ social functioning: hint of an added benefit – extent: “minor”	Health-related quality of life ▪ symptoms (physical functioning) ▫ < 65 years: hint of lesser benefit – extent: “minor”
	Serious/severe side effects ▪ severe AEs (CTCAE grade 3–4): ▫ ISS staging (stage I): hint of greater harm – extent “major” ▪ febrile neutropenia: hint of greater harm – extent: “minor”
Non-serious/non-severe symptoms/late complications ▪ symptoms (insomnia): ▫ ISS stage II: hint of an added benefit – extent: “considerable” ▪ symptoms (diarrhoea): ▫ ethnicity (Caucasian): hint of an added benefit – extent: “minor”	Non-serious/non-severe side effects ▪ gastrointestinal disorders and respiratory disorders: hint of greater harm – extent: “minor” ▪ thoracic and mediastinal disorders: hint of greater harm – extent: “minor”
AE: adverse event; CTCAE: Common Terminology Criteria of Adverse Events; ISS: International Staging System	

The overall assessment showed both positive and negative effects – partly also in subgroups – with differences in the certainty of results (indication or hints) for daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone.

The results showed an effect modification by sex for the outcome “overall survival”. For women, this resulted in an indication of a major added benefit for this outcome. For men, the added benefit is not proven for this outcome. Under consideration of the positive and negative effects, the overall conclusion on the added benefit was therefore derived separately for women and men. In the overall consideration, positive effects outweigh negative effects for women, whereas for men, positive and negative effects are overall balanced. This is due to the fact that the hints of greater harm on the side of negative effects mostly have the extent “minor”. The outcome “severe AEs” (CTCAE grade 3–4) in patients with ISS stage I is an exception as there is greater harm with the extent “major”. However, since there was no information how the effects regarding this outcome are in men or women with this ISS

stage I, this effect cannot be meaningfully interpreted in the balancing of positive and negative effects.

In summary, there is an indication of a major added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone for women with multiple myeloma who have received at least one prior therapy. For men with multiple myeloma who have received at least one prior therapy, there is, in summary, no hint of an added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone; the added benefit is therefore not proven.

2.3.4 List of included studies

Dimopoulos MA, Oriol A, Nahi H, San-Miguel J, Bahlis NJ, Usmani SZ et al. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med 2016; 375(14): 1319-1331.

Janssen Research & Development. A study comparing daratumumab, lenalidomide, and dexamethasone with lenalidomide and dexamethasone in relapsed or refractory multiple myeloma: full text view [online]. In: ClinicalTrials.gov. 28.07.2017 [Accessed: 11.10.2017]. URL: https://clinicaltrials.gov/ct2/show/NCT02076009.

Janssen Research & Development. Phase 3 study comparing daratumumab, lenalidomide, and dexamethasone (DRd) vs lenalidomide and dexamethasone (Rd) in subjects with relapsed or refractory multiple myeloma: study MMY3003; clinical protocol [unpublished]. 2016.

Janssen Research & Development. Phase 3 study comparing daratumumab, lenalidomide, and dexamethasone (DRd) vs lenalidomide and dexamethasone (Rd) in subjects with relapsed or refractory multiple myeloma: study MMY3003; statistical analysis plan [unpublished]. 2016.

Janssen Research & Development. Phase 3 study comparing daratumumab, lenalidomide, and dexamethasone (DRd) vs lenalidomide and dexamethasone (Rd) in subjects with relapsed or refractory multiple myeloma: studyMMY3003; clinical study report [unpublished]. 2016.

Janssen Research & Development. Phase 3 study comparing daratumumab, lenalidomide, and dexamethasone (DRd) vs lenalidomide and dexamethasone (Rd) in subjects with relapsed or refractory multiple myeloma: study MMY3003; Zusatzanalysen [unpublished]. 2017.

Janssen-Cilag International. Phase 3 study comparing daratumumab, lenalidomide, and dexamethasone (DRd) vs lenalidomide and dexamethasone (Rd) in subjects with relapsed or refractory multiple myeloma [online]. In: EU Clinical Trials Register. [Accessed: 12.06.2017]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-005525-23.

2.4 Research question 2: adult patients with relapsed and refractory multiple myeloma

2.4.1 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 daratumumab (status: 12 June 2017)
- bibliographical literature search on daratumumab (last search on 19 June 2017)
- search in trial registries for studies on daratumumab (last search on 12 June 2017)
- bibliographical literature search on ACTs (last search on 19 June 2017)
- search in trial registries for studies on ACTs (last search on 12 June 2017)

To check the completeness of the study pool:

- search in trial registries for studies on daratumumab (last search on 23 August 2017)

The check identified no additional relevant study.

Concurring with the company, the check of the completeness of the study pool produced no RCTs on the comparison of daratumumab with the ACT.

Since no RCTs of direct comparisons were available, the company conducted an information retrieval for further investigations. Based on the search results, the company identified further investigations, which it used for the benefit assessment. This was the single-arm study SIRIUS [19] for daratumumab and the retrospective observational study IMF cohort [20] for the ACT. The company presented the single-arm daratumumab study MMY3010 [21] as additional information (see Section 2.6.2.3.2 of the full dossier assessment).

The data presented by the company were unsuitable to draw conclusions on the added benefit of daratumumab in comparison with the ACT. This is justified below.

Further investigations on daratumumab

The SIRIUS study was the approval study of daratumumab in the present therapeutic indication. It was a single-arm, multi-part, phase 2 dose-ranging study. The SIRIUS study included patients with multiple myeloma who had received at least 3 prior therapies, including a PI and an IMiD, or who were refractory to both a PI and an IMiD. The company presented analyses of those patients (N = 106) who were receiving approval-compliant treatment with daratumumab over the total study period. Overall response was the primary outcome of the study. Further outcomes were overall survival and side effects. The study started on 30 September 2013 and ended on 30 May 2017.

Further investigations on the appropriate comparator therapy

As further investigation on the ACT, the company identified the retrospective observational study IMF cohort. The IMF cohort consisted of patients retrospectively identified from patient charts (N = 543) from North America, Europe and Asia. It included patients with relapsed multiple myeloma who had received at least 3 prior therapies and who were refractory to both a PI and an IMiD. The retrospective observation period started at the time point when a patient fulfilled all these criteria. Of the patients included in the cohort, 462 patients received further therapies. The patients received individual treatment specified by the physician. All subsequent treatment regimens and the number of the lines of treatment were documented. There was on information on the dosages used, however; hence it remained unclear whether the treatments were administered in compliance with the SPCs. No information on further treatment was available for 81 of 543 (15%) patients included in the study. It was unclear whether they were treated with best supportive care (BSC) as comprised by the ACT. Overall survival was the primary outcome of the study. The study started in June 2015 and is ongoing.

Results of the total IMF cohort are reported in the publication Kumar 2017. Individual patient data of the IMF cohort were available to the company for its dossier. The company's results were primarily based on analyses of the patients from Germany (N = 28). As sensitivity analysis, the company additionally presented the results of patients (N = 234) from Europe who were treated with substances approved in Germany.

It remained unclear why the company only used a subpopulation of the IMF cohort for its analyses. In principle, the total IMF cohort would be relevant for the benefit assessment.

Similarity of the study populations questionable

For the IMF cohort, the information on the characteristics of the study population was not available for all characteristics. The information provided by the company for patients from Germany or Europe were not interpretable because they referred to lines of treatment and not to individual patients (see next section). The median age showed no difference between the patients in the SIRIUS study and the total IMF cohort. Whereas the proportion of men and women was balanced in the SIRIUS study, more men (about 60%) than women (about 40%) were included in the IMF cohort. The median time since the first diagnosis was 4.8 years in the SIRIUS study and 3.1 years in the IMF cohort. There was only some information on disease-specific characteristics for the IMF cohort. The ISS stage was unknown in about 56% of the patients in the IMF cohort, for example. No information was provided for the IMF cohort on ECOG PS, type of myeloma, cytogenetic profile, number of lytic bone lesions and extramedullary plasmacytomas, or on myeloma-related osteopenia. The number of prior therapies was comparable between the groups; the median number was 5 therapies in the SIRIUS study and 4 therapies in the IMF cohort. Regarding pretreatment, there was a notable difference between the patients in the studies regarding the characteristic of previous autologous stem cell transplantation. In the SIRIUS study, about 80% of the patients had already received autologous stem cell transplantation before the study, whereas this was the

case for only 48% of the patients in the IMF cohort. There was no information for the IMF cohort regarding prior chemotherapies, steroid therapies and radiotherapy. All patients in both studies had been pretreated with both a PI and an IMiD and showed refractoriness to both substance classes. In summary, no certain assessment of the similarity of both study populations was possible.

Results presented by the company

Overall survival

The analyses presented by the company for the outcome "overall survival" could not be used for the dossier assessment. The main reason was that the company did not consider individual patients in its analyses of the IMF cohort, but the number of the lines of treatment. For instance, the 28 German patients were included in the analysis as 54 lines of treatment. The number of the patients and lines of treatment included in the analyses of the IMF cohort presented by the company and of the events for the outcome "overall survival" are presented in Table 19.

Table 19: Analyses of the IMF cohort presented by the company for the outcome "overall survival"

IMF cohort	Patients from Germany	Patients from Europe
Number of patients	28	234
Number of the lines of treatment	54	338
Events for the outcome "overall survival" based on the number of patients	ND	ND
Events for the outcome "overall survival" based on the number of the lines of treatment	40	203
IMF: International Myeloma Foundation; ND: no data		

For 28 patients of the IMF cohort from Germany, the analyses presented by the company resulted in 40 events for the outcome "overall survival". These analyses are inadequate and hence unsuitable for the benefit assessment. Analyses based on actually observed patients are required, as the ones presented by the company for its daratumumab study SIRIUS. The company did not present this type of analysis, however. Furthermore, it remained unclear why the company limited its analyses to patients from Germany and Europe and did not use the total IMF cohort.

In the present case, this was a comparison of individual arms from different studies. In such a case, the effect must be so large that it cannot be caused by systematic bias alone to allow the derivation of an added benefit. Irrespective of the fact that the similarity of the study populations also cannot be estimated with certainty, the comparison of the median survival times in the SIRIUS study (18.6 months; 95% confidence interval [CI] [13.7; 25.0]) with that of the total IMF cohort (13.0 months; 95% CI [11.1; 14.5]) showed no effect large enough to derive an added benefit. It has to be considered that it was unclear for 81 of 543 patients in the

IMF cohort whether they received treatment (BSC) in the sense of the ACT. If only those patients in the IMF cohort who received at least one further line of treatment are considered, the difference shown between the groups is even smaller (18.6 months; 95% CI [13.7; 25.0] in the SIRIUS study versus 15.2 months; 95% CI [13.2; 17.0] in the IMF cohort [N = 462 patients who received at least one further line of treatment]).

Morbidity and health-related quality of life

No patient-relevant outcomes in the categories "morbidity" and "health-related quality of life" were recorded in the SIRIUS study and in the IMF cohort.

Side effects

The company provided a comprehensive report of the side effects in the SIRIUS study. For the IMF cohort, results only for the outcome "discontinuation due to AEs" were available only for patients from Germany and Europe. However, the company again only presented analyses based on lines of treatment. These analyses were inadequate (see above).

Summary

No added benefit of daratumumab in comparison with the ACT could be derived from the data of further investigations presented by the company. The similarity of the study populations of the SIRIUS study and the IMF cohort could not be assessed with certainty. The analyses presented by the company based on lines of treatment were inadequate. Irrespective of this, there was no effect large enough for the outcome "overall survival" between the SIRIUS study and the IMF cohort to derive an added benefit. No comprehensive consideration of the positive and negative effects of daratumumab was possible because data on the comparison with the ACT were only available for the outcomes "overall survival" and "discontinuation due to AEs".

2.4.2 Results on added benefit

The company presented no usable data for the assessment of the added benefit of daratumumab in comparison with the ACT for adults with relapsed and refractory multiple myeloma, whose prior therapy included a PI and an IMiD, and who have demonstrated disease progression on the last therapy. This resulted in no hint of an added benefit in comparison with the ACT. An added benefit is therefore not proven.

2.4.3 Probability and extent of added benefit

The data presented by the company for the assessment of the added benefit of daratumumab in adults with relapsed and refractory multiple myeloma, whose prior therapy included a PI and an IMiD, and who have demonstrated disease progression on the last therapy, were unsuitable to derive an added benefit. Hence an added benefit of daratumumab is not proven for these patients.

2.4.4 List of included studies

Not applicable as the company presented no relevant data for the benefit assessment.

2.5 Probability and extent of added benefit – summary

Table 20: Daratumumab – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	Daratumumab in combination with lenalidomide and dexamethasone, or in combination with bortezomib and dexamethasone: adult patients with multiple myeloma who have received at least one prior therapy[b]	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	For daratumumab in combination with bortezomib and dexamethasone: ▪ added benefit not proven For daratumumab in combination with lenalidomide and dexamethasone: men: Added benefit not proven women: indication of major added benefit
2	Daratumumab as monotherapy: adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a PI and an IMiD, and who have demonstrated disease progression on the last therapy[c]	Individual treatment specified by the physician under consideration of prior therapies, duration and extent of the response, and the approval of the drugs[d]	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: It is assumed for the present therapeutic indication that the use of daratumumab in combination with lenalidomide and dexamethasone, or in combination with bortezomib and dexamethasone, is conducted in the framework of a remission-inducing induction treatment. High-dose chemotherapy with stem cell transplantation, which may be a subsequent treatment option, is therefore not an option as part of the ACT.
c: It is assumed for the present therapeutic indication that high-dose chemotherapy with stem cell transplantation is not an option for the patients at the time point of their current treatment.
d: This also includes BSC, which ensures best possible supportive therapy, optimized for the individual patient, for alleviation of symptoms and improvement in the quality of life.
ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; IMiD: immunomodulatory drug; PI: proteasome inhibitor

The assessment described above deviates from that of the company, which overall derived an indication of a considerable added benefit for adults with multiple myeloma who have received at least one prior therapy (research question 1). The company claimed a hint of an added benefit with the extent non-quantifiable, but at least considerable, for adults with relapsed and refractory multiple myeloma, whose prior therapy included a PI and an IMiD, and who have demonstrated disease progression on the last therapy (research question 2).

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

Supplementary note

The result of the assessment deviates from the result of the G-BA assessment in the framework of the market access in 2016. In this assessment, the G-BA had determined a non-quantifiable added benefit of daratumumab for adults with relapsed and refractory multiple myeloma, whose prior therapy included a PI and an IMiD, and who have demonstrated disease progression on the last therapy (research question 2). However, in this assessment, the added benefit had been regarded as proven by the approval because of the special situation for orphan drugs, irrespective of the underlying data.

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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