IQWiG Reports – Commission No. A22-40

Daratumumab (multiple myeloma) –

Benefit assessment according to §35a Social Code Book V[1] (Expiry of the limitation period)

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: 28 June 2022). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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

Patient and family involvement

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

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

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ASCT	autologous SCT
CTCAE	Common Technology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HLT	High Level Term
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ISS	International Staging System
NRE	not recorded elsewhere
PFS	progression-free survival
RCT	randomized controlled trial
SCT	stem cell transplantation
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug daratumumab in combination with lenalidomide and dexamethasone or bortezomib + dexamethasone). The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 1 April 2022.

The time limit was set because the assessment was based on an interim analysis of the studies CASTOR and POLLUX and the data on overall survival showed a low number of events at the time of the data cut-off on 30 June 2016. In accordance with the commission, the current benefit assessment refers exclusively to research question A of the first assessment (adult patients with multiple myeloma who have already received at least 1 therapy).

Research question

The aim of the present report is the assessment of the added benefit of daratumumab 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 who have received at least one prior therapy.

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

Table 2: Research question of the benefit assessment of daratumumab in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone

Therapeutic indication	**ACT**[a]
Adult patients with multiple myeloma who have received at least one prior therapy[b, c]	Bortezomib in combination with pegylated liposomal doxorubicin or bortezomib in combination with dexamethasone or lenalidomide in combination with dexamethasone or elotuzumab in combination with lenalidomide and dexamethasone or carfilzomib in combination with lenalidomide and dexamethasone or carfilzomib in combination with dexamethasone
a. Presented is the ACT specified by the G-BA. The company did not restrict the inclusion criteria for the search for studies relevant to the assessment with regard to the drugs, but included all drugs named by the G-BA. b. It is assumed that high-dose chemotherapy with stem cell transplantation was not an option for the patients at the time point of their current treatment. c. It is assumed that the special situation of refractory patients will be taken into account when choosing the ACT. G-BA: Federal Joint Committee	

The company followed the G-BA's specification on the ACT, but additionally cited the options daratumumab in combination with lenalidomide and dexamethasone as well as daratumumab in combination with bortezomib and dexamethasone. This has no consequence for the benefit assessment, as only data on options named by the G-BA (lenalidomide in combination with dexamethasone and bortezomib in combination with dexamethasone) are available for the benefit assessment.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) are used for the derivation of the added benefit. This concurs with the company's inclusion criteria. However, the company made a restriction with regard to the proportion of events achieved in the outcome "overall survival" and only included studies in which this proportion was higher than in the studies POLLUX and CASTOR at the time of the first assessment. This approach is not appropriate. The results of all relevant studies in the therapeutic indication are to be used.

Study pool and study design

The studies CASTOR und POLLUX were included in the benefit assessment. Deviating from the company, the LEPUS study is also considered relevant and used for the assessment. The study pool submitted by the company for the benefit assessment is therefore incomplete, but it can be estimated with sufficient certainty that the overall assessment of the present benefit assessment is not called into question by the LEPUS study (see below).

CASTOR

The CASTOR study is a randomized, controlled, open-label study 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.

Randomization of the patients was stratified by International Staging System (ISS) stage at screening (I, II or III), the number of prior lines of treatment (1 versus 2 or 3 versus > 3) and prior bortezomib treatment (no versus yes). 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 (SCT). In the study, 61% of the patients had received autologous SCT (ASCT) before study

inclusion; this was unclear for the remaining 39%. However, the inclusion criteria of the CASTOR study can be considered adequate and in line with the German health care context.

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

POLLUX

The POLLUX study is a randomized, controlled, open-label approval study on the comparison of daratumumab + lenalidomide + dexamethasone with lenalidomide + dexamethasone alone.

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.

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. Dexamethasone, in contrast, was used in a lower dosage than recommended in the SPC of lenalidomide for the present therapeutic indication. The POLLUX study is used for the benefit assessment despite the deviating dosage of dexamethasone.

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

LEPUS

As the CASTOR study, LEPUS is a randomized, controlled, open-label study 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. The inclusion and exclusion criteria as well as the other study and intervention characteristics largely correspond to those of the CASTOR study.

The LEPUS study is still ongoing and is conducted at study centres in China and Taiwan. 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 treatment with bortezomib (no versus yes) to the daratumumab or the comparator arm (141 versus 70 patients) in a 2:1 ratio.

The investigated outcomes correspond to those in the CASTOR study.

Risk of bias

The risk of bias across outcomes was rated as low for the studies CASTOR, POLLUX and LEPUS. At outcome level, the risk of bias of the results on the outcome "overall survival" in the studies CASTOR and POLLUX was assessed as low. For all other outcomes, the risk of bias of the results was rated as high for both studies. For the outcome of severe AEs (CTCAE grade ≥ 3), a high certainty of results is assumed despite the high risk of bias due to incomplete observation for potentially informative reasons, as the effect is essentially determined by events occurring very early in the course of the study and is not questioned by censoring due to progression events occurring later. There are no usable data from the LEPUS study.

Results

Usability of the results and analyses of the LEPUS study

In Module 4 A, the company presented no prepared data for the LEPUS study. Therefore, no prepared data are available from LEPUS for the benefit assessment in Module 4 A. Moreover, the clinical study report only contains data on overall survival for the second data cut-off relevant for the assessment; data on side effects and morbidity as well as on quality of life are missing. Furthermore, usable data on side effects are also lacking for the first data cut-off, as the necessary event time analyses are missing. Due to this incompleteness, the results of the LEPUS study were not used for the derivation of the added benefit. The impact of the missing data on the statements on the added benefit at outcome level in the categories of morbidity, health-related quality of life and side effects cannot be conclusively assessed. However, due to the smaller number of patients included compared to the studies CASTOR and POLLUX and the similar results on overall survival, it is assumed that the results of the LEPUS study do not call into question the overall consideration of the present benefit assessment.

Mortality

Overall survival

The meta-analysis of the studies CASTOR and POLLUX showed a statistically significant difference in favour of daratumumab between the treatment groups for the outcome "overall survival". As a result, there was proof of an added benefit of daratumumab in comparison with the ACT.

Morbidity

Health status (EQ-5D VAS)

For the outcome "health status", the meta-analysis of the studies CASTOR and POLLUX does not show any statistically significant difference between the treatment groups. This resulted in no hint of an added benefit of daratumumab in comparison with the ACT for the outcome "health status"; an added benefit is therefore not proven.

Symptoms (EORTC QLQ-C30)

Symptom outcomes were recorded using the EORTC QLQ-C30 symptom scales. The meta-analysis of the studies CASTOR and POLLUX showed no statistically significant difference between the treatment groups for each of the following outcomes: fatigue, nausea and vomiting, pain, dyspnoea, insomnia, loss of appetite, constipation and diarrhoea. This resulted in no hint of an added benefit of daratumumab in comparison with the ACT for these outcomes; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

Outcomes on health-related quality of life were recorded with the EORTC QLQ-C30 functional scales. The meta-analysis of the studies CASTOR and POLLUX showed no statistically significant difference between the treatment groups for each of the following outcomes: global health status, physical functioning, role functioning, emotional functioning, and cognitive functioning. This resulted in no hint of an added benefit of daratumumab in comparison with the ACT for these outcomes; an added benefit is therefore not proven.

For the outcome “social functioning”, the meta-analysis of the studies CASTOR and POLLUX shows no statistically significant difference between the treatment groups, but there is an effect modification by the characteristic “age”. This results in an indication of an added benefit of daratumumab versus the ACT for patients ≥ 65 years of age. For patients < 65 years, there was no hint of an added benefit of daratumumab versus the ACT; an added benefit is therefore not proven for these patients.

Side effects

SAEs

For the outcome “SAEs”, the meta-analysis of the studies CASTOR and POLLUX does not show any statistically significant difference between the treatment arms. For the outcome “SAEs”, there was no hint of greater or lesser harm from daratumumab in comparison with the ACT; greater or lesser harm is therefore not proven.

Severe AEs

The meta-analysis of the studies CASTOR and POLLUX showed a statistically significant difference to the disadvantage of daratumumab in comparison with the ACT for the outcome "severe AEs". For both studies, high certainty of results was assumed despite the high risk of bias. However, there was an effect modification by the characteristic of ISS stage. This resulted in a proof of greater harm from daratumumab versus the ACT for patients with ISS stage I. For patients in ISS stages II and III, there is no hint of greater or lesser harm from daratumumab versus the ACT; greater or lesser harm is arm is therefore not proven for these patients.

Discontinuation due to AEs (at least one drug component)

The meta-analysis showed no statistically significant difference between the treatment arms for the outcome "discontinuation due to AEs (at least one drug component)". This resulted in no hint of greater or lesser harm from daratumumab in comparison with the ACT for the outcome "discontinuation due to AEs"; greater or lesser harm is therefore not proven.

Infusion related reactions

The analyses presented by the company for the outcome "infusion related reaction" are not suitable for the benefit assessment. However, the events on which infusion-related reactions are based are covered by the specific AEs.

This resulted in no hint of greater or lesser harm from daratumumab in comparison with the ACT; greater or lesser harm is therefore not proven.

Peripheral neuropathy not recorded elsewhere (NRE) (High Level Term [HLT], severe AEs)

As a specific AE of bortezomib, the outcome "peripheral neuropathy NRE (HLT, severe AEs)" is of particular interest only for patients treated with bortezomib. There was no statistically significant difference between the treatment arms in the CASTOR study. This resulted in no hint of greater or lesser harm from daratumumab + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone for this outcome; greater or lesser harm is therefore not proven.

Specific AEs

Vomiting (Preferred Term [PT], AEs), blood and lymphatic system disorders (System Organ Class [SOC], severe AEs), respiratory, thoracic and mediastinal disorders (SOC, severe AEs), diarrhoea (PT, severe AEs), hypertension (PT, severe AEs)

The meta-analysis of the studies CASTOR and POLLUX shows a statistically significant difference to the disadvantage of daratumumab versus the ACT for each of the following outcomes: vomiting (PT, AEs), blood and lymphatic system disorders (SOC, severe AEs), respiratory, thoracic and mediastinal disorders (SOC, severe AEs), diarrhoea (PT, severe AEs) and hypertension (PT, severe AEs). This results in an indication of greater harm from daratumumab in comparison with the ACT for each of these 5 specific AEs.

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 overall assessment shows both positive and negative effects with different extents for daratumumab compared with the ACT.

On the side of the positive effects, there is proof of an added benefit with the extent "considerable" for the outcome "overall survival". For patients ≥ 65 years, there is also an indication of minor added benefit in the outcome "social functioning".

The negative effects exclusively refer to outcomes in the category of AEs: the total rate of severe AEs with the extent "major" for patients in ISS stage I, as well as 5 specific AEs, some with the extent "considerable", some with the extent "minor" for the total population. There is proof of greater harm for "severe AEs"; indications of greater harm were derived for each of the specific AEs. The negative effects refer exclusively to the shortened period until the end of treatment (plus a maximum of 30 days).

The effects described are based on the results of the studies CASTOR and POLLUX; the LEPUS study provided no usable data.

Thus, a positive effect in the outcome "overall survival" with the extent "considerable" is offset by negative effects in the outcome category of side effects, of which the total rate of severe AEs with the extent "major" is of particular importance for patients in ISS stage I due to the high certainty of conclusions. Regarding magnitude and certainty of conclusions, the advantage in the outcome "social functioning" for patients ≥ 65 years is secondary to the advantage in overall survival for the total population and therefore does not influence the overall assessment. The negative effects do not completely challenge the positive effect for the outcome "overall survival"; however, in the overall consideration, they influence the extent of the added benefit. This is regarded as considerable for patients in ISS stages II and III, and as minor for patients in ISS stage I due to the disadvantage in the outcome "severe AEs".

It is assumed that the results of the LEPUS study do not challenge this overall assessment.

In summary, there is proof of considerable added benefit of daratumumab versus the ACT for adults with ISS stage II or III multiple myeloma who have received at least one prior therapy, and proof of minor added benefit of daratumumab versus the ACT for adults with ISS stage I multiple myeloma who have received at least one prior therapy.

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

The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Daratumumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with multiple myeloma who have received at least one prior therapy[b, c]	Bortezomib in combination with pegylated liposomal doxorubicin or bortezomib in combination with dexamethasone or lenalidomide in combination with dexamethasone or elotuzumab in combination with lenalidomide and dexamethasone or carfilzomib in combination with lenalidomide and dexamethasone or carfilzomib in combination with dexamethasone	Patients with ISS stage II or III: ▪ proof of considerable added benefit
		Patients with ISS stage I: ▪ proof of minor added benefit

a. Presented is the ACT specified by the G-BA. The company did not restrict the inclusion criteria for the search for studies relevant to the assessment with regard to the drugs, but included all drugs named by the G-BA.
b. It is assumed that high-dose chemotherapy with stem cell transplantation was not an option for the patients at the time point of their current treatment.
c. It is assumed that the special situation of refractory patients will be taken into account when choosing the ACT.

G-BA: Federal Joint Committee

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

2.2 Research question

The aim of the present report is the assessment of the added benefit of daratumumab in combination with lenalidomide and dexamethasone or in combination with bortezomib and dexamethasone in comparison with the ACT in adult patients with multiple myeloma who have received at least one prior therapy.

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

Table 4: Research question of the benefit assessment of daratumumab in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone

Therapeutic indication	**ACT[a]**
Adult patients with multiple myeloma who have received at least one prior therapy[b, c]	Bortezomib in combination with pegylated liposomal doxorubicin or bortezomib in combination with dexamethasone or lenalidomide in combination with dexamethasone or elotuzumab in combination with lenalidomide and dexamethasone or carfilzomib in combination with lenalidomide and dexamethasone or carfilzomib in combination with dexamethasone
a. Presented is the ACT specified by the G-BA. The company did not restrict the inclusion criteria for the search for studies relevant to the assessment with regard to the drugs, but included all drugs named by the G-BA. b. It is assumed that high-dose chemotherapy with stem cell transplantation was not an option for the patients at the time point of their current treatment. c. It is assumed that the special situation of refractory patients will be taken into account when choosing the ACT. G-BA: Federal Joint Committee	

The company followed the G-BA's specification on the ACT, but additionally cited the options daratumumab in combination with lenalidomide and dexamethasone as well as daratumumab in combination with bortezomib and dexamethasone. This has no consequence for the benefit assessment, as only data on options named by the G-BA (lenalidomide in combination with dexamethasone and bortezomib in combination with dexamethasone) are available for the benefit assessment.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs are used for the derivation of the added benefit. This concurs with the company’s inclusion criteria. However, the company made a restriction with regard to the proportion of events achieved in the outcome “overall survival” and only included studies in which this proportion was higher than in the studies POLLUX and CASTOR at the time of the first assessment. This approach is not appropriate. The results of all relevant studies in the therapeutic indication are to be used (see also Section 2.3).

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on daratumumab (status: 03 February 2022)
- bibliographical literature search on daratumumab (last search on 03 February 2022)
- search in trial registries/trial results databases for studies on daratumumab (last search on 3 February 2022)
- search on the G-BA website for daratumumab (last search on 3 February 2022)

To check the completeness of the study pool:

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

Besides the studies POLLUX and CASTOR, the check of the completeness of the company's study pool identified one additional study relevant for the benefit assessment, i.e. the LEPUS study.

Relevance of the LEPUS study for the present assessment

The RCT LEPUS included adult patients with multiple myeloma who had shown disease progression after at least one prior therapy and were not refractory to a proteasome inhibitor. The study compared daratumumab + bortezomib + dexamethasone with bortezomib + dexamethasone. The LEPUS study is still ongoing and is exclusively conducted at study centres in China and Taiwan. The final data cut-off is planned after 140 deaths or 3 years after randomization of the last patient and is not yet available. Clinical study reports are available for each of the previous data cut-offs (first interim analysis: 7 October 2019; second interim analysis: 30 July 2021). Thus, the LEPUS study meets all inclusion criteria for the present benefit assessment.

Although the company identified the LEPUS study it conducted, it did not use it in Module 4 A for the benefit assessment. It justified this by stating that it was an ongoing study for which final results were not yet available. The results from the first data cut-off of 7 October 2019 were not relevant due to the low number of events in the outcome "overall survival" (14.7% of randomized patients), as final results were available from the studies POLLUX and CASTOR, which currently represent the best available evidence. The results of the second data cut-off of 30 July 2021 had become available too shortly before the dossier submission to be able to use them for the benefit assessment.

The company's reasoning is not appropriate. While it is true that this is an ongoing study in the therapeutic indication (study start: November 2017; planned study end: September 2022), this

is not a reason for exclusion, as results from 2 data cut-offs are already available. The corresponding clinical study report on the 2nd data cut-off shows the date 11 February 2022. The results available so far should have been taken into account in the dossier.

Overall, the study pool presented by the company for the benefit assessment is incomplete. Moreover, usable data are not available for all relevant outcomes in the LEPUS study (see Section 2.4.1). The LEPUS study is nevertheless considered for the benefit assessment and the influence of the study on the assessment is estimated (see Section 2.4.1). The results of the study available in the dossier are presented as supplementary information in Appendix F of the full dossier assessment. The decisive factor for this procedure is that it can be estimated with sufficient certainty that the overall assessment of the present benefit assessment is not called into question by the LEPUS study (see Section 2.4.1).

2.3.1 Studies included

The studies listed in the following Table 5 were included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: daratumumab arm vs. comparator arm

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
MMY3004 (CASTOR[d])	Yes	Yes	No	Yes [3-6]	Yes [7-9]	Yes [10-16]
MMY3003 (POLLUX[d])	Yes	Yes	No	Yes [17-20]	Yes [21-23]	Yes [14-16,24-27]
MMY3009 (LEPUS[d])	Yes[e]	Yes	No	Yes [28,29]	Yes [30]	Yes [31]

a. Study for which the company was sponsor.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the tables below, the study will be referred to using this acronym.
e. In the approval process, the company submitted the LEPUS study to the National Medical Products Administration, formerly the China Food and Drug Administration.

RCT: randomized controlled trial

2.3.2 Study characteristics

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

Table 6: Characteristics of the studies included – RCT, direct comparison: daratumumab arm vs. comparator arm (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
CASTOR	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 + bortezomib + dexamethasone (N = 251) bortezomib + dexamethasone (N = 247)	Screening: ≤ 21 days before the first cycle treatment: until disease progression or occurrence of unacceptable toxicity observation[c]: until death, end of study, or withdrawal of consent	117 centres in Australia, Brazil, Czech Republic, Germany, Hungary, Italy, Korea, Mexico, Netherlands, Poland, Russia, Sweden, Spain, Turkey, Ukraine, USA 09/2014–ongoing first data cut-off: 11 January 2016 second data cut-off: 30 June 2016 third data cut-off: 28 June 2021	Primary: PFS secondary: overall survival, morbidity, health-related quality of life, AEs
POLLUX	RCT, open-label, parallel	Adults (≥ 18 years) with multiple myeloma who have received at least one prior therapy[d] 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[c]: outcome-specific, at most until death, 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 06/2014–ongoing first data cut-off: 07 March 2016 second data cut-off: 30 June 2016 second data cut-off: 30 September 2021	Primary: PFS secondary: overall survival, symptoms, health status, health-related quality of life, AEs

Table 6: Characteristics of the studies included – RCT, direct comparison: daratumumab arm vs. comparator arm (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
LEPUS	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 + bortezomib + dexamethasone (N = 141) bortezomib + dexamethasone (N = 70)	Screening: ≤ 21 days before randomization treatment: until disease progression or occurrence of unacceptable toxicity observation[c]: until death, end of study, or withdrawal of consent	27 centres in China, Taiwan 12/2017–ongoing first data cut-off: 07 October 2019 second data cut-off: 30 July 2021	Primary: PFS secondary: overall survival, morbidity, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on 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 refractoriness to protease inhibitors (PI) (e.g. bortezomib, ixazomib and carfilzomib) or intolerance to bortezomib were excluded from the study.
c. Outcome-specific information is provided in Table 8.
d. 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; CD38: cluster of differentiation 38; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; PFS: progression-free survival; PI: protease inhibitor; N: number of randomized patients; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: daratumumab arm vs. comparator arm (multipage table)

Study	Intervention	Comparison
CASTOR	Daratumumab 16 mg/kg BW IV[a]: ▪ cycles 1–3: day 1, 8 and 15 ▪ cycles 4–8: day 1 ▪ from cycle 9: day 1 + bortezomib 1.3 mg/m² BSA SC: ▪ cycles 1–8: day 1, 4, 8 and 11 + dexamethasone 20 mg oral[b], cycles 1–8: ▪ < 75 years: day 1, 2, 4, 5, 8, 9, 11 and 12 ▪ ≥ 75 years or BMI < 18.5[c]: 20 mg/week ▪ 1 cycle is 3 weeks	Bortezomib 1.3 mg/m² BSA SC: ▪ cycles 1–8: day 1, 4, 8 and 11 + ▪ dexamethasone 20 mg oral, cycles 1–8: ▪ < 75 years: day 1, 2, 4, 5, 8, 9, 11 and 12 ▪ ≥ 75 years or BMI < 18.5[c]: 20 mg/week ▪ 1 cycle is 3 weeks
	Treatment adjustments ▪ dose adjustments for daratumumab not allowed[d] ▪ dose adjustments for bortezomib allowed in case of AEs ▪ dose reduction or discontinuation for dexamethasone allowed in case of AEs (to 40 mg/week and thereafter to 20 mg/week) **Premedication before daratumumab** ▪ dexamethasone[b] 20 mg IV or orally (or equivalent dose of an intermediate or long-acting corticoid) ▪ paracetamol (acetaminophen) 650 to 1000 mg IV or orally ▪ antihistamine (diphenhydramine 25–50 mg or equivalent) ▪ optional: leukotriene inhibitor (such as montelukast 10 mg IV or orally on day 1 of a cycle) The oral premedication can be taken at home if administered up to 3 hours before the daratumumab infusion **Postmedication after daratumumab** patients with a higher risk of respiratory complications[e] 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 or ± long-acting bronchodilators such as tiotropium or salmeterol for COPD **Concomitant treatment** ▪ concomitant medication for the treatment of infusion-related reactions ▪ growth factors (e.g. CSF), platelet or erythrocyte transfusions ▪ anti-infectives (e.g. for the treatment of *Pneumocystitis carinii* and herpes zoster) ▪ bisphosphonates for patients with myeloma-related bone disorder ▪ 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 ▪ concurrent treatment with strong CYP3A4 inhibitors or inducers should be avoided	

Table 7: Characteristics of the intervention – RCT, direct comparison: daratumumab arm vs. comparator arm (multipage table)

Study	Intervention	Comparison
POLLUX	Daratumumab 16 mg/kg BW IV[a]: ▪ 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[f] (≤ 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 is 30 to 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[d] ▪ dose adjustments for lenalidomide in accordance with the SPC allowed ▪ dose reduction or discontinuation for dexamethasone allowed in case of AEs **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[e] 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 (such as salbutamol) inhaled corticosteroids ± long-acting beta 2 adrenergic receptor agonists for asthma ± long-acting bronchodilators such as tiotropium or salmeterol for COPD **Concomitant treatment** ▪ concomitant medication for the treatment of infusion-related reactions ▪ growth factors (e.g. CSF), platelet or erythrocyte transfusions ▪ anti-infectives (e.g. for the treatment of *Pneumocystitis carinii* and herpes zoster) ▪ 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) ▪ 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	

Table 7: Characteristics of the intervention – RCT, direct comparison: daratumumab arm vs. comparator arm (multipage table)

Study	Intervention	Comparison
LEPUS	see CASTOR[g]	

a. As of Amendment 6 (CASTOR) or Amendment 8 (POLLUX) of the study protocol (each in April 2020), daratumumab can also be administered in a fixed dose of 1800 mg.
b. Dexamethasone was administered as premedication on the days of the daratumumab infusion: IV before the first daratumumab infusion, thereafter, oral administration was also possible.
c. And in patients with poorly controlled diabetes mellitus or previous intolerance of or AE as reaction to steroid therapy.
d. In case of IRR, and depending on the severity, the infusion is interrupted until stabilization, the infusion speed is adjusted or treatment is stopped.
e. E.g. COPD patients with FEV1 < 80% or with mild asthma.
f. On the day of the administration of daratumumab, half of the dexamethasone dose was administered IV or orally 1 to 3 hours before the daratumumab infusion; the other half was taken orally on the next day.
g. In addition to the options available in the CASTOR study, leukotriene inhibitors could also be used in the post-medication phase in the LEPUS study.

AE: adverse event; BSA: body surface area; 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: intravenous; NSAID: nonsteroidal anti-inflammatory drug; RCT: randomized controlled trial; SC: subcutaneous

Study CASTOR

The CASTOR study is already known from a previous benefit assessment procedure [14,15]. The CASTOR study is a randomized, controlled, open-label study 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 ECOG PS of 0 to 2. Patients with refractoriness or intolerance to bortezomib were excluded.

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 bortezomib treatment (no versus yes). 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 within both study arms was performed in accordance with the SPC of daratumumab [32,33] or bortezomib [34]. 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 SCT [34]. In the study, 61% of the patients had received ASCT before study inclusion; this was unclear for the remaining 39%. The CASTOR study was therefore at first not used for the benefit assessment [14]. However, the commenting procedure and the oral hearing showed that the inclusion criteria of the CASTOR study could be considered adequate and corresponding to the German health care context [35,36]. Therefore, the G-BA had commissioned the reassessment of the CASTOR study [15].

The primary outcome of the study was PFS. Relevant secondary outcomes were "overall survival", "symptoms", "health-related quality of life" and AEs.

Study POLLUX

The POLLUX study is also already known from a previous benefit assessment procedure [14,15]. The POLLUX study is a randomized, controlled, open-label approval study on the comparison of daratumumab + lenalidomide + dexamethasone with lenalidomide + dexamethasone alone.

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.

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 [32,33,37]. Dexamethasone, in contrast, was used in a lower dosage than recommended in the SPC of lenalidomide for the present therapeutic indication [37]. This fact was also described in detail in dossier assessment A17-40 [14]. The POLLUX study is used for the benefit assessment despite the deviating dosage of dexamethasone.

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

Study LEPUS

As the CASTOR study, LEPUS is a randomized, controlled, open-label study 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 (see also Section 2.3). The inclusion and exclusion criteria as well as the other study and intervention characteristics largely correspond to those of the CASTOR study.

The LEPUS study is still ongoing and is conducted at study centres in China and Taiwan. 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 treatment with bortezomib (no versus yes) to the daratumumab or the comparator arm (141 versus 70 patients) in a 2:1 ratio.

The investigated outcomes correspond to those in the CASTOR study.

Data cut-offs and analyses

There are 3 data cut-offs for each of the studies CASTOR and POLLUX. For the present benefit assessment, only the respective final data cut-off is relevant, which, as prespecified, took place in both studies when 320 or 330 events in the outcome "overall survival" were achieved. The final data cut-off was carried out on 28 June 2021 for the CASTOR study, and on 30 September 2021 for the POLLUX study.

Two data cut-offs are available for the LEPUS study. The first data cut-off of 7 October 2019 had been prespecified as interim analysis and contains data on all relevant outcomes. The reason for the second data cut-off of 30 July 2021 is not fully clear from the available documents. However, based on the available information, it is assumed that this is the final PFS analysis and thus a prespecified data cut-off. For this data cut-off, the company only analysed data relevant for the benefit assessment for the outcome "overall survival"; however, it is not clear from the dossier that the recording of data for other outcomes has already been completed. For the other patient-relevant outcomes, the dossier only provides analyses for the first data cut-off, but time-adjusted responder analyses are also missing here.

Planned duration of follow-up observation

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

Table 8: Planned duration of follow-up observation – RCT, direct comparison: daratumumab vs. comparator arm

Study **outcome category** **outcome**	**Planned follow-up observation**
CASTOR	
Mortality	
Overall survival	Until death
Morbidity	
Symptoms/ health status (EORTC QLQ-C30 symptom scales, EQ-5D VAS)	Week 8 and 16 after discontinuation of treatment or until progression, start of a new antitumour treatment or death
Health-related quality of life (EORTC QLQ-C30)	Week 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 of side effects	Up to 30 days after the last dose of the study medication or until start of a new antitumour treatment
POLLUX	
Mortality	
Overall survival	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)	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 of side effects	Up to 30 days after the last dose of the study medication or start of a new antitumour treatment
LEPUS	see CASTOR

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

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). For these outcomes, data are therefore available only for the shortened observation period. However, to be able to draw a reliable conclusion on the total study period or the time to patient death, it would be necessary to record these outcomes as well for the total period, as was done for survival.

Characteristics of the study populations

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

Table 9: Characteristics of the study population as well as discontinuation of the study/treatment – RCT, direct comparison: daratumumab arm vs. comparator arm (multipage table)

Study characteristic category	CASTOR		POLLUX		LEPUS	
	Daratumumab + bortezomib + dexamethasone	Bortezomib + dexamethasone	Daratumumab + lenalidomide + dexamethasone	Lenalidomide + dexamethasone	Daratumumab + bortezomib + dexamethasone	Bortezomib + dexamethasone
	N[a] = 251	N[a] = 247	N[a] = 286	N[a] = 283	N[a] = 141	N[a] = 70
Age [years], mean (SD)	63 (10)	64 (10)	64 (9)	64 (9)	60 (9)	62 (9)
Sex [F/M], %	45/55	41/59	40/60	42/58	40/60	40/60
Family origin n (%)						
White	216 (86)	219 (89)	207 (72)	186 (66)	0 (0)	0 (0)
Black, African American	14 (6)	6 (2)	5 (2)	11 (4)	0 (0)	0 (0)
Asian	12 (5)	11 (4)	54 (19)	46 (16)	141 (100)	70 (100)
Other[b]	9 (4)[c]	11 (4)[c]	20 (7)[c]	40 (14)[c]	0 (0)	0 (0)
ECOG PS, n (%)						
0	106 (42)	116 (47)	139 (49)	150 (53)	64 (45)	27 (39)
1	131 (52)	112 (45)	136 (48)	118 (42)	70 (50)	35 (50)
2	13 (5)	19 (8)	11 (4)	15 (5)	7 (5)	8 (11)
Myeloma type, n (%)						
IgG	136 (54)	148 (60)	164 (57)	167 (59)	62 (44)	32 (46)
IgA	59 (24)	54 (22)	55 (19)	56 (20)	34 (24)	13 (19)
IgM	1 (0)	1 (0)	2 (1)	0 (0)	0 (0)	2 (3)
IgD	6 (2)	3 (1)	5 (2)	6 (2)	7 (5)	4 (6)
IgE	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Free light chains (FLC)	43 (17)	36 (15)	55 (19)	46 (16)	37 (26)	19 (27)
FLC kappa	30 (12)	17 (7)	34 (12)	32 (11)	16 (11)	12 (17)
FLC lambda	13 (5)	19 (8)	21 (7)	14 (5)	21 (15)	7 (10)
Biclonal	2 (1)	3 (1)	1 (0)	0 (0)	0 (0)	0 (0)
Negative immune fixation	4 (2)	2 (1)	4 (1)	8 (3)	0 (0)	0 (0)

Table 9: Characteristics of the study population as well as discontinuation of the study/treatment – RCT, direct comparison: daratumumab arm vs. comparator arm (multipage table)

Study characteristic category	CASTOR		POLLUX		LEPUS	
	Daratumumab + bortezomib + dexamethasone	Bortezomib + dexamethasone	Daratumumab + lenalidomide + dexamethasone	Lenalidomide + dexamethasone	Daratumumab + bortezomib + dexamethasone	Bortezomib + dexamethasone
	N[a] = 251	N[a] = 247	N[a] = 286	N[a] = 283	N[a] = 141	N[a] = 70
ISS stage[d], n (%)						
I	98 (39)	96 (39)	137 (48)	140 (49)	72 (51)	34 (49)
II	94 (37)	100 (40)	93 (33)	86 (30)	45 (32)	22 (31)
III	59 (24)	51 (21)	56 (20)	57 (20)	24 (17)	14 (20)
Disease duration: time from first diagnosis of the multiple myeloma until randomization [years], mean (SD)	4.7 (3.2)	4.8 (3.3)	4.6 (3.6)	4.8 (3.6)	4.1 (2.3)	3.8 (2.5)
Prior therapies, n (%)	251 (100)	247 (100)	286 (100)	283 (100)	141 (100)	70 (100)
Prior systemic treatment	251 (100)	247 (100)	286 (100)	283 (100)	141 (100)	70 (100)
Prior ASCT	156 (62)	149 (60)	180 (63)	180 (64)	29 (21)	13 (19)
Prior radiotherapy	63 (25)	59 (24)	65 (23)	57 (20)	9 (6)	3 (4)
Number of prior therapies, n (%)						
1	122 (49)	113 (46)	149 (52)	146 (52)	41 (29)	19 (27)
2	70 (28)	74 (30)	85 (30)	80 (28)	45 (32)	25 (36)
3	37 (15)	32 (13)	38 (13)	38 (13)	25 (18)	8 (11)
> 3	22 (9)	28 (11)	14 (5)	19 (7)	30 (21)	18 (26)
Prior PI, n (%)	169 (67)	172 (70)	245 (86)	242 (86)	112 (79)	57 (81)
Bortezomib	162 (65)	164 (66)	241 (84)	238 (84)	110 (78)	57 (81)
Carfilzomib	12 (5)	10 (4)	6 (2)	6 (2)	2 (1)	0 (0)
Ixazomib	12 (5)	7 (3)	2 (1)	2 (1)	0 (0)	1 (1)
Prior IMiD, n (%)	179 (71)	198 (80)	158 (55)	156 (55)	130 (92)	64 (91)
Lenalidomide	89 (35)	120 (49)	50 (17)	50 (18)	48 (34)	26 (37)
Pomalidomide	7 (3)	7 (3)	2 (1)	0 (0)	3 (2)	2 (3)

Table 9: Characteristics of the study population as well as discontinuation of the study/treatment – RCT, direct comparison: daratumumab arm vs. comparator arm (multipage table)

Study characteristic category	CASTOR		POLLUX		LEPUS	
	Daratumumab + bortezomib + dexamethasone	Bortezomib + dexamethasone	Daratumumab + lenalidomide + dexamethasone	Lenalidomide + dexamethasone	Daratumumab + bortezomib + dexamethasone	Bortezomib + dexamethasone
	N[a] = 251	N[a] = 247	N[a] = 286	N[a] = 283	N[a] = 141	N[a] = 70
Thalidomide	125 (50)	121 (49)	122 (43)	125 (44)	116 (82)	56 (80)
Treatment discontinuation[e], n (%)	213 (88)[c, f]	104 (44)[c, f]	208 (73[c])[g]	259 (92[c])[g]	105 (75)[h, i]	35 (51)[h, i]
Study discontinuation, n (%)	164 (65)[c, j]	195 (79)[c, j]	168 (59)[c, k]	193 (68)[c, k]	55 (39)[h, l]	38 (54)[h, l]

a. Number of randomized patients.
b. "Other" comprises the following groups: American Indian or native Alaskan, Hawaiian or Pacific, other, unknown, and not reported.
c. Institute's calculation.
d. Based on the levels of serum beta 2 microglobulin and albumin.
e. It is unclear in each case whether the data refer to the discontinuation of all or of any of the drug components.
f. Common reasons for the treatment discontinuation were not given.
g. Common reasons for treatment discontinuation in the daratumumab versus the comparator arm were: disease progression (40% vs. 64%), AEs (20% vs. 17%), non-compliance with intervention (4% vs. 2 %).
h. The data shown refer to the data cut-off of 30 July 2021.
i. Common reasons for treatment discontinuation in the daratumumab versus the comparator arm were: disease progression (60% vs. 32%), AEs (4% vs. 9%), adverse events (5% vs. 3 %).
j. Common reasons for study discontinuation in the daratumumab versus the comparator arm were: death (59% vs. 69%), withdrawal of consent (4% vs. 8%).
k. Common reasons for study discontinuation in the daratumumab versus the comparator arm were: death (54% vs. 61%) and withdrawal of consent (4% vs. 6%).
l. Common reasons for study discontinuation in the daratumumab versus the comparator arm were: death (34% vs. 40%) and withdrawal of consent (3% vs. 9%).

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

CASTOR

The patient characteristics were largely comparable between the treatment groups of the CASTOR study. Most patients were white; the mean age was 64 years. 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 stages I and II and had an ECOG PS of 0 or 1. About 61% of the patients had received prior ASCT.

At the time point of the final data cut-off, 213 (88%) of the patients in the daratumumab arm had discontinued treatment; this was the case for 104 (44%) of the patients in the comparator arm. The higher proportion of treatment discontinuations in the daratumumab arm is plausible, as treatment with daratumumab is to be continued until progression, whereas treatment with bortezomib + dexamethasone in the comparator arm ends after 8 3-week cycles (see Table 7).

POLLUX

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 stages I and II and had an ECOG PS of 0 or 1. About 63% of the patients had received prior ASCT.

There were notable differences between the study arms in treatment discontinuation, however. At the time point of the final data cut-off, 208 (73%) patients in the daratumumab arm and 259 (92%) patients in the comparator arm had discontinued the study. The treatment discontinuations in both arms were largely due to disease progression (40 % of the patients in the daratumumab arm and 64 % in the comparator arm).

LEPUS

In the LEPUS study, the patient characteristics are also comparable between the treatment groups. The patients were almost exclusively of Asian family origin; the mean age in the daratumumab arm was 60 years and in the comparator arm 62 years. Here again, the proportion of men (60%) was somewhat higher in both study arms than the proportion of women (40%). According to the inclusion criteria, all patients had received at least one systemic treatment for multiple myeloma before study inclusion. More than 70% of the patients were pretreated with 2 or more therapies. The majority of the patients included were allocated to ISS stages I and II and had an ECOG PS of 0 or 1. Only about 20% of the patients had received prior ASCT.

At the time point of the second data cut-off, 105 (75%) patients in the daratumumab arm had discontinued treatment; this was the case for 35 (51%) patients in the comparator arm. The higher proportion of treatment discontinuations in the daratumumab arm is plausible, as

treatment with daratumumab is to be continued until progression, whereas treatment with bortezomib + dexamethasone in the comparator arm ends after 8 3-week cycles (see Table 7).

Comparability of the study populations of the studies included

The patients in all 3 included studies are comparable in numerous relevant characteristics. This concerns in particular age, gender, ECOG PS, ISS stage and disease duration. Apart from the fact that all patients in the LEPUS study are of Asian family origin, while this only applies to 5% or 18% of the patients in CASTOR and POLLUX respectively, there are clear differences regarding other characteristics between CASTOR and POLLUX on the one hand and LEPUS on the other. In the LEPUS study, for example, significantly fewer patients had received ASCT (20% compared to 61% and 63% in CASTOR and POLLUX). Moreover, fewer patients were pretreated with radiotherapy. However, in the LEPUS study, more than 70% of patients had already received 2 or more prior therapies before inclusion in the study, compared to about half in each of the studies CASTOR and POLLUX.

Overall, the similarities between the study populations of all 3 studies included in the assessment outweigh the differences. Therefore, the results of the studies can be summarized using a fixed-effect model.

Course of the study

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

Table 10: Information on the course of the study – RCT, direct comparison: daratumumab arm vs. comparator arm (multipage table)

Study **duration of the study phase** **outcome category**	**Daratumumab arm**	**Comparator arm**
CASTOR (data cut-off: 28 June 2021)		
Treatment duration [months]	N = 243[a]	N = 237[a]
Median [min; max]	13.4 [0.0; 79.7]	5.2 [0.2; 8.0]
Mean (SD)	24.0 (23.9)	4.2 (1.7)
Observation period [months]	N = 251	N = 247
Overall survival[b]		
Median [min; max]	72.5 [0.1; 79.8]	72.6 [0.0; 78.1]
Mean (SD)	44.0 (27.3)	36.4 (26.8)
Morbidity, health-related quality of life		
EQ-5D		
Median [min; max]	16.1 [ND]	6.9 [ND]
Mean (SD)	ND	ND
EORTC QLQ-C30		
Median [min; max]	16.1 [ND]	6.9 [ND]
Mean (SD)	ND	ND
Side effects	N = 243[a]	N = 237[a]
Median [min; max]	14.3 [ND]	6.2 [ND]
Mean (SD)	ND	ND
POLLUX (data cut-off: 30 September 2021)		
Treatment duration [months]	N = 283[a]	N = 281[a]
Median [min; max]	34.3 [0.0; 85.0]	16.0 [0.2; 86.2]
Mean (SD)	42.4 (29.7)	23.9 (23.3)
Observation period [months]	N = 286	N = 283
Overall survival[b]		
Median [min; max]	79.9 [0.0; 86.5]	79.4 [0.1; 86.3]
Mean (SD)	53.5 (28.1)	47.7 (28.7)
Morbidity, health-related quality of life		
EQ-5D		
Median [min; max]	35.2 [ND]	17.6 [ND]
Mean (SD)	ND	ND
EORTC QLQ-C30		
Median [min; max]	35.1 [ND]	17.6 [ND]
Mean (SD)	ND	ND
Side effects	N = 283[a]	N = 281[a]
Median [min; max]	35.3 [ND]	16.9 [ND]
Mean (SD)	ND	ND

Table 10: Information on the course of the study – RCT, direct comparison: daratumumab arm vs. comparator arm (multipage table)

Study duration of the study phase outcome category	Daratumumab arm	Comparator arm
LEPUS (data cut-off: 30 July 2021)		
Treatment duration [months]	N = 140[a]	N = 68[a]
Median [min; max]	13.0 [0.0; 40.5]	5.2 [0.0; 37.4]
Mean (SD)	15.6 (10.8)	8.4 (9.1)
Observation period [months]	N = 141	N = 70
Overall survival [b]		
Median [min; max]	26.0 [0.1; 42.1]	21.7 [0.0; 40.7]
Mean (SD)	20.6 (10.0)	14.9 (10.2)
Morbidity, health-related quality of life, side effects	ND	ND

a. For treatment duration, only patients who have received treatment are analysed.
b. The calculation was probably made using the inverse Kaplan-Meier method [38].

EORTC: European Organisation for Research and Treatment of Cancer; max: maximum; min: minimum; N: number of analysed patients; ND: no data; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SD: standard deviation

The median treatment durations differ significantly between the daratumumab arm and the comparator arm in all 3 included studies. Between the studies CASTOR and LEPUS (second data cut-off), which each compared daratumumab + bortezomib + dexamethasone with bortezomib + dexamethasone, the median treatment durations of the respective arms are similar (approx. 13 months vs. approx. 5 months). In the POLLUX study, which compared daratumumab + lenalidomide + dexamethasone with lenalidomide + dexamethasone, the median treatment durations are significantly longer (34 and 16 months).

The median observation time for the outcome “overall survival” was approximately the same in all studies in the study arms, only in the second data cut-off of the LEPUS study, the comparison group was observed for a slightly shorter time of 22 months than the intervention group with 26 months. For all other outcomes, the observation times in the studies CASTOR and POLLUX were significantly shorter overall compared to the observation time of the outcome “overall survival” and also differed greatly between the treatment groups, with shorter observation times in the comparison arms. For the LEPUS study, information on the observation duration is only available for the outcome “overall survival”.

Subsequent therapies

Table 11 shows the subsequent therapies patients received after discontinuing the study medication.

Table 11: Information on subsequent therapies directed against the multiple myeloma (≥ 5% of the patients in ≥ 1 treatment arm) – RCT, direct comparison: daratumumab arm vs. comparator arm (multipage table)

Study drug class drug	Patients with subsequent therapy n (%)	
	daratumumab arm	comparator arm
CASTOR[a]	**N = 243**	**N = 237**
Total (patients with ≥ 1 subsequent therapy)	161 (66.3)	200 (84.4)
≥ 1 ASCT	13 (5.3)	9 (3.8)
Corticosteroids for systemic use	152 (62.6)	172 (72.6)
Dexamethasone	144 (59.3)	157 (66.2)
Prednisone	11 (4.5)	23 (9.7)
Prednisolone	11 (4.5)	21 (8.9)
Other antineoplastic agents	104 (42.8)	158 (66.7)
Daratumumab	11 (4.5)	125 (52.7)
Carfilzomib	51 (21.0)	59 (24.9)
Bortezomib	48 (19.8)	55 (23.2)
Ixazomib	20 (8.2)	23 (9.7)
Cisplatin	14 (5.8)	12 (5.1)
Alkylating agents	88 (36.2)	109 (46.0)
Cyclophosphamide	68 (28.0)	80 (33.8)
Melphalan	25 (10.3)	35 (14.8)
Bendamustine	20 (8.2)	27 (11.4)
Herbal alkaloids and other natural remedies	21 (8.6)	20 (8.4)
Etoposide	14 (5.8)	13 (5.5)
Cytotoxic antibiotics and related substances	19 (7.8)	21 (8.9)
Doxorubicin	18 (7.4)	19 (8.0)
Immunosuppressants	133 (54.7)	163 (68.8)
Lenalidomide	97 (39.9)	109 (46.0)
Pomalidomide	56 (23.0)	76 (32.1)
Thalidomide	28 (11.5)	30 (12.7)
Investigational preparations	16 (6.6)	12 (5.1)
POLLUX[a]	**N = 283**	**N = 281**
Total (patients with ≥ 1 subsequent therapy)	127 (44.9)	210 (74.7)
≥ 1 ASCT[b]	11 (3.9)	13 (4.6)
Other antineoplastic agents	101 (35.7)	183 (65.1)
Bortezomib	56 (19.8)	95 (33.8)
Daratumumab	19 (6.7)	122 (43.4)
Carfilzomib	47 (16.6)	66 (23.5)
Ixazomib	8 (2.8)	25 (8.9)
Cisplatin	14 (4.9)	16 (5.7)

Table 11: Information on subsequent therapies directed against the multiple myeloma (≥ 5% of the patients in ≥ 1 treatment arm) – RCT, direct comparison: daratumumab arm vs. comparator arm (multipage table)

Study **drug class** **drug**	**Patients with subsequent therapy n (%)**	
	daratumumab arm	**comparator arm**
Alkylating agents	63 (22.3)	121 (43.1)
Cyclophosphamide	50 (17.7)	107 (38.1)
Melphalan	20 (7.1)	39 (13.9)
Bendamustine	10 (3.5)	26 (9.3)
Herbal alkaloids and other natural remedies	17 (6.0)	24 (8.5)
Etoposide	14 (4.9)	21 (7.5)
Cytotoxic antibiotics and related substances	15 (5.3)	22 (7.8)
Doxorubicin	14 (4.9)	22 (7.8)
Corticosteroids for systemic use	115 (40.6)	184 (65.5)
Dexamethasone	111 (39.2)	177 (63.0)
Prednisone	4 (1.4)	20 (7.1)
Prednisolone	9 (3.2)	14 (5.0)
Immunosuppressants	90 (31.8)	143 (50.9)
Pomalidomide	67 (23.7)	104 (37.0)
Lenalidomide	27 (9.5)	52 (18.5)
Thalidomide	19 (6.7)	30 (10.7)
LEPUS	ND	

a. Safety population.
b. Presented for the comparability with the CASTOR study, although below the threshold value.

n: number of patients with subsequent therapy; N: number of analysed patients; ND: no data; RCT: randomized controlled trial

In the CASTOR study, a large proportion (about 75%) of patients with progression had received at least one subsequent therapy directed against the multiple myeloma by the final data cut-off. Taking into account the higher proportion of patients with subsequent therapy in the comparator arm, there were no noticeable differences in the various subsequent therapies. More than half of the patients in the comparator arm received daratumumab as subsequent therapy. However, it is not clear from the data submitted by the company in which combination daratumumab was used.

In the POLLUX study, too, the majority (approx. 60%) of patients with progression had received at least one subsequent therapy directed against the multiple myeloma at the final data cut-off, whereby a higher proportion of patients in the comparator arm received a subsequent therapy here as well. Again, there were no noticeable differences in the various subsequent therapies. About 43% of the patients in the comparator arm received daratumumab as subsequent therapy.

For the LEPUS study, information on subsequent therapies is only available for the first data cut-off of 7 October 2019. No information is available for the data cut-off of 30 July 2021, which is principally relevant for the assessment.

Risk of bias across outcomes (study level)

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: daratumumab arm vs. comparator arm

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
CASTOR	Yes	Yes	No	No	Yes	Yes	Low
POLLUX	Yes	Yes	No	No	Yes	Yes	Low
LEPUS	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for all studies.

Limitations resulting from the open-label study design are described in Section 2.4 with the outcome-specific risk of bias.

Transferability of the study results to the German health care context

In the opinion of the company, the results of the studies CASTOR and POLLUX are transferable to the German health care context. Both studies had been carried out in the European Union as well as in the USA and Canada. In both studies, the majority of patients were of "Caucasian family origin" (CASTOR: 87%, POLLUX 70%). According to the company, there were no indications of biodynamic or kinetic differences between the individual population groups or countries involved and Germany to the extent that they would have a significant impact on the study results. Therefore, it could be assumed that the results, taking into account the uncertainty associated with the transferability of clinical data, are in principle transferable to the German health care context.

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

The company presented no information on the transferability of the results from the LEPUS study to the German health care context.

2.4 Results on added benefit

2.4.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - symptoms measured with the EORTC QLQ-C30 symptom scales
  - health status measured using 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 AEs (SAEs)
  - severe AEs (Common Technology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to AEs (at least one drug component)
  - infusion related reaction
  - peripheral neuropathy (NRE), (HLT, severe AEs); only for patients treated with bortezomib
  - further specific AEs, if any

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

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

Table 13: Matrix of outcomes – RCT, direct comparison: daratumumab arm vs. comparator arm

Study	Outcomes									
	Overall survival	Health status (EQ-5D VAS)	Symptoms (EORTC QLQ-C30 symptom scales)	Health-related quality of life (EORTC QLQ-C30 functional scales)	SAEs	Severe AEs[a]	Discontinuation due to AEs (≥ 1 drug component)	Infusion related reactions	Peripheral neuropathies[b]	Further specific AEs[a, c]
CASTOR	Yes	Yes	Yes	Yes	Yes[d]	Yes[d]	Yes	No[e]	Yes	Yes
POLLUX	Yes	Yes	Yes	Yes	Yes[d]	Yes[d]	Yes	No[e]	No	Yes
LEPUS	No usable data[f]									

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. Specific AE for bortezomib, therefore irrelevant for the POLLUX study.
c. The following events were considered (MedDRA coding): "vomiting (PT, AEs)", "blood and lymphatic system disorders (SOC, severe AEs)", "respiratory, thoracic and mediastinal disorders (SOC, severe AEs)", "diarrhoea (PT, severe AEs)" and "hypertension (PT, severe AEs)".
d. Although the SOC "neoplasms benign, malignant and unspecified (including cysts and polyps)" are included in the outcomes on side effects, the majority of these are secondary primary tumours (e.g. squamous cell carcinoma).
e. The analysis presented by the company is not suitable for the benefit assessment; however, the events underlying the outcome are recorded via the specific AEs. For reasons, see the following section.
f. Module 4 A provides no prepared data from the LEPUS study (see the following section), moreover, the dossier contains no usable data on side effects and morbidity/quality of life for the second data cut-off, which is principally relevant for the assessment. Due to this incompleteness, the results of the LEPUS study were not used for the derivation of the added benefit; selected available results are presented as supplementary information in Appendix F of the full dossier assessment.

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; MedDRA: Medical Dictionary for Regulatory Activities; n: no; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Notes on outcomes and analyses

Response criteria for the scales of the EORTC QLQ-C30 and the EQ-5D VAS (studies CASTOR and POLLUX)

In its dossier, the company presented EORTC QLQ-C30 responder analyses for the proportion of patients with a change ≥ 10 points (respective scale range: 0 to 100). As explained in the *General Methods* of the Institute [39,40], for a response criterion to reflect with sufficient certainty a change noticeable for the patient, it should correspond to a predefined value of at least 15% of the scale range of an instrument (in post-hoc analyses exactly 15% of the scale range). For the EORTC QLQ-C30 and its additional modules, the analysis with a response

threshold of 10 points is considered a sufficient approximation to an analysis with a 15% threshold (15 points) and is used for the benefit assessment (for explanation see Appendix B of the full dossier assessment).

The company used 15 points as threshold for the analyses of the EQ-5D VAS. This corresponds to 15% of the instrument's scale range.

Event time analyses for the EORTC QLQ-C30 scales and the EQ-5D VAS (studies CASTOR and POLLUX)

For the outcomes on health status, symptoms and health-related quality of life (recorded with the EORTC QLQ-C30 scales and the EQ-5D VAS), the company submitted event time analyses. For each outcome, Module 4 A presents analyses of time to first improvement, confirmed permanent improvement, first deterioration and confirmed permanent deterioration by the response criteria described above. In Module 4 A, the company defines the confirmed permanent deterioration as a deterioration by at least the threshold value (≥ 15 points for the EQ-5D VAS and ≥ 10 points for the scales of the EORTC QLQ-C30) compared to baseline, for which the response criterion is considered fulfilled in all subsequent observations until the end of the observation.

As described in Section 2.3.2, the observation period for the outcomes on health status, symptoms and health-related quality of life is, on the one hand, systematically shortened with regard to median overall survival and, on the other hand, differs significantly between the treatment arms of the respective studies (see Table 8 and Table 10). This results in difficulties in the interpretation of the analysis of the time to permanent (confirmed) improvement or deterioration, which are explained in detail in dossier assessment A21-153 [1].

Due to the progressive course of the disease to be expected in the present therapeutic indication and taking into account in particular the distribution of the absolute scale values at baseline, an analysis of the deterioration of the health status is primarily required for the present benefit assessment.

For these reasons, the event time analyses for the time to first deterioration were used for the present benefit assessment.

Infusion related reactions

The analyses presented by the company for the outcome "infusion-related reaction" are not suitable for the benefit assessment. An infusion-related reaction was documented as event related to the infusion of daratumumab in the case report form (CRF) of the included studies CASTOR, POLLUX and LEPUS. However, since administration of placebo infusions was impossible in the comparator arm, these events could only occur in the intervention arm. A comparison between the study arms is therefore not possible on the basis of this outcome. In Module 4 A, the company describes for the CASTOR and POLLUX studies that infusion-related reactions were predominantly assigned to the system organ classes (SOCs) "general

disorders and administration site conditions" as well as "respiratory, thoracic and mediastinal disorders".

In the studies included, the events underlying the outcome "infusion-related reactions" are also included in the analyses on AEs (overall rates and specific AEs). The fact that individual specific AEs are symptoms of an infusion-related reaction follows from the plausibility of the symptoms for a cytokine release syndrome (e.g. Preferred Term [PT] dyspnoea, cough, irritated throat and bronchospasm from the SOC "respiratory, thoracic and mediastinal disorders") as well as from the typically early occurrence at the time of the first infusion with daratumumab (see Kaplan-Meier curves in Appendix D of the full dossier assessment). If these specific AEs show a statistically significant difference between the treatment groups and the frequency limits shown in Appendix E of the full dossier assessment are exceeded, the events underlying the outcome "infusion-related reaction" are thus mapped in the benefit assessment via the specific AEs (see Table 15).

Usability of the results and analyses of the LEPUS study

In Module 4 A, the company presented no prepared data for the LEPUS study. Therefore, no prepared data are available from LEPUS for the benefit assessment in Module 4 A. Moreover, the clinical study report only contains data on overall survival for the second data cut-off relevant for the assessment; data on side effects and morbidity as well as on quality of life are missing. Furthermore, usable data on side effects are also lacking for the first data cut-off, as the necessary event time analyses are missing. Due to this incompleteness, the results of the LEPUS study were not used for the derivation of the added benefit and are presented as supplementary information in Appendix F of the full dossier assessment. The impact of the missing data on the statements on the added benefit at outcome level in the categories of morbidity, health-related quality of life and side effects cannot be conclusively assessed. However, due to the lower number of patients included compared to the studies CASTOR and POLLUX (211 versus 1067 patients) and the similar results on overall survival (pooled hazard ratio [HR] from CASTOR and POLLUX: 0.74; HR from LEPUS: 0.67, see Table 32 of the full dossier assessment), it is assumed that the results of the LEPUS study do not call into question the overall assessment (see Section 2.5.2) of the present benefit assessment.

2.4.2 Risk of bias

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

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: daratumumab arm vs. comparator arm

Study	Study level	Outcomes									
		Overall survival	Health status (EQ-5D VAS)	Symptoms (EORTC QLQ-C30 symptom scales)	Health-related quality of life (EORTC QLQ-C30 functional scales)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Infusion related reactions	Peripheral neuropathies[b]	Further specific AEs[a, c]
CASTOR	N	N	H[d, e]	H[d, e]	H[d, e]	H[f]	H[f]	H[d]	–[g]	H[f]	H[f]
POLLUX	N	N	H[d, e]	H[d, e]	H[d, e]	H[f]	H[f]	H[d]	–[g]	–	H[f]
LEPUS	N	No usable data[h]									

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. Specific AE for bortezomib, therefore irrelevant for the POLLUX study.
c. The following events were considered (MedDRA coding): "vomiting (PT, AEs)", "blood and lymphatic system disorders (SOC, severe AEs)", "respiratory, thoracic and mediastinal disorders (SOC, severe AEs)", "diarrhoea (PT, severe AEs)" and "hypertension (PT, severe AEs)".
d. Lack of blinding in subjective recording of outcomes.
e. Notable differences in the questionnaire return rate between the treatment arms.
f. Incomplete observations for potentially informative reasons.
g. The analysis presented by the company is not suitable for the benefit assessment; however, the events underlying the outcome are recorded via the specific AEs. See Section 2.4.1 of the present benefit assessment for reasons.
h. Module 4 A of the full dossier assessment provides no processed data from the LEPUS study (see the previous Section 2.4.1); moreover, the dossier contains no usable data on side effects and morbidity/quality of life for the second data cut-off, which is principally relevant for the analysis. Due to this incompleteness, the results of the LEPUS study were not used for the derivation of the added benefit; selected available results are presented as supplementary information in Appendix F of the full dossier assessment.

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-C30; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

The risk of bias of the results on the outcome "overall survival" in the studies CASTOR and POLLUX was assessed as low.

The risk of bias in the studies CASTOR and POLLUX 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 the questionnaire return rate between both arms of the individual studies. Due to incomplete observation for potentially informative reasons, the risk of bias for the outcomes of SAEs, severe AEs (CTCAE grade ≥ 3) and for the specific AEs was also rated as high. The same risk

of bias arised for the outcome "discontinuation due to AEs" due to the lack of blinding in subjective recording of outcomes. A high certainty of results was assumed for the outcome "severe AEs (CTCAE grade ≥ 3)" despite the high risk of bias. The reason is that most events related to this outcome occurred very early in the course of the study (see Figure 27 and Figure 55 of the full dossier assessment). In contrast, a relevant extent of progression events of the underlying disease, which usually lead to treatment discontinuation and thus also to a discontinuation of the observation, only occurred much later in the course of the study (see the Kaplan-Meier curves for PFS, Figure 36 and Figure 60 of the full dossier assessment). The effect is thus not called into question by the censoring that occurs later due to progression events. This can be assessed with sufficient certainty on the basis of the Kaplan-Meier curves for the total population also for the subgroups considered in Section 2.4.4.

There are no usable data from the LEPUS study. The outcome-specific risk of bias of the results was therefore not assessed.

2.4.3 Results

Table 15 summarizes the results on the comparison of daratumumab in combination with lenalidomide and dexamethasone or in combination with bortezomib and dexamethasone (daratumumab arm) versus lenalidomide in combination with dexamethasone or with bortezomib in combination with dexamethasone (comparator arm) in patients with multiple myeloma who have already received at least 1 prior therapy. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. Fixed-effect models were chosen for the meta-analyses. With the exception of the respective concomitant and control treatment, the studies CASTOR and POLLUX had a very similar design, and the reported effects were clearly homogeneous for almost all the outcomes considered. The figures of the meta-analyses can be found in Appendix C of the full dossier assessment. The Kaplan-Meier curves on the included outcomes are presented in Appendix D of the full dossier assessment, and the results on common AEs, SAEs, severe AEs and discontinuations due to AEs can be found in Appendix E of the full dossier assessment. Results from the LEPUS study are presented as supplementary information in Appendix F of the full dossier assessment.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: daratumumab arm vs. comparator arm (multipage table)

Outcome category outcome study	Daratumumab arm N	Daratumumab arm median time to event in months [95% CI] patients with event n (%)	Comparator arm N	Comparator arm median time to event in months [95% CI] patients with event n (%)	Daratumumab arm vs. comparator arm HR [95% CI]; p-value[a]
Mortality					
Overall survival					
CASTOR[b, c]	251	49.6 [42.2; 62.3] 148 (59.0)	247	38.5 [31.2; 46.2] 171 (69.2)	0.74 [0.59; 0.92]; 0.008
POLLUX[d, e]	286	67.6 [53.1; 80.5] 153 (53.5)	283	51.8 [44.0; 60.0] 175 (61.8)	0.73 [0.58; 0.91]; 0.005
Total					0.74 [0.63; 0.86]; < 0.001[f]
Morbidity					
Health status (EQ-5D VAS)[g]					
CASTOR[b, c]	251	10.1 [5.6; 28.2] 115 (45.8)	247	6.4 [4.4; NC] 98 (39.7)	0.88 [0.66; 1.16]; 0.366
POLLUX[d, e]	286	11.2 [7.9; 21.1] 145 (50.7)	283	11.6 [8.9; 18.6] 129 (45.6)	1.02 [0.80; 1.30]; 0.896
Total					0.96 [0.80; 1.15]; 0.647[f]
Symptoms (EORTC QLQ-C30)[h]					
Fatigue					
CASTOR[b, c]	251	1.5 [1.5; 2.1] 180 (71.7)	247	2.1 [1.5; 2.9] 151 (61.1)	1.10 [0.88; 1.38]; 0.379
POLLUX[d, e]	286	1.9 [1.3; 2.0] 203 (71.0)	283	2.0 [1.9; 2.8] 193 (68.2)	1.08 [0.89; 1.33]; 0.431
Total					1.09 [0.94; 1.26]; 0.266[f]
Nausea and vomiting					
CASTOR[b, c]	251	6.8 [5.0; 9.7] 133 (53.0)	247	NA [7.9; NC] 79 (32.0)	1.31 [0.98; 1.74]; 0.069
POLLUX[d, e]	286	13.0 [9.3; 16.9] 156 (54.5)	283	10.2 [5.8; 15.6] 145 (51.2)	0.89 [0.70; 1.12]; 0.309
Total					1.04 [0.87; 1.25]; 0.677[f]
Pain					
CASTOR[b, c]	251	3.5 [2.8; 4.0] 156 (62.2)	247	3.6 [2.8; 4.9] 125 (50.6)	1.04 [0.82; 1.33]; 0.738
POLLUX[d, e]	286	5.6 [3.8; 10.3] 176 (61.5)	283	5.6 [3.7; 7.5] 174 (61.5)	0.89 [0.72; 1.11]; 0.298
Total					0.95 [0.81; 1.12]; 0.566[f]

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: daratumumab arm vs. comparator arm (multipage table)

Outcome category outcome study	Daratumumab arm N	Daratumumab arm median time to event in months [95% CI] patients with event n (%)	Comparator arm N	Comparator arm median time to event in months [95% CI] patients with event n (%)	Daratumumab arm vs. comparator arm HR [95% CI]; p-value[a]
Dyspnoea					
CASTOR[b, c]	251	3.6 [2.8; 4.9] 145 (57.8)	247	2.9 [2.3; 4.3] 128 (51.8)	0.92 [0.72; 1.18]; 0.512
POLLUX[d, e]	286	4.7 [2.9; 6.6] 176 (61.5)	283	5.7 [3.8; 8.4] 168 (59.4)	1.02 [0.82; 1.26]; 0.876
Total					0.98 [0.83; 1.15]; 0.766[f]
Insomnia					
CASTOR[b, c]	251	2.4 [2.1; 3.5] 152 (60.6)	247	2.9 [2.1; 5.7] 118 (47.8)	1.08 [0.84; 1.39]; 0.538
POLLUX[d, e]	286	6.6 [4.7; 9.2] 163 (57.0)	283	3.8 [2.9; 5.8] 171 (60.4)	0.83 [0.67; 1.03]; 0.092
Total					0.93 [0.79; 1.09]; 0.367[f]
Appetite loss					
CASTOR[b, c]	251	5.0 [4.2; 6.9] 138 (55.0)	247	6.0 [4.6; 7.0] 109 (44.1)	1.06 [0.82; 1.38]; 0.632
POLLUX[d, e]	286	7.2 [4.9; 10.3] 170 (59.4)	283	9.6 [5.3; 14.1] 148 (52.3)	1.12 [0.90; 1.40]; 0.317
Total					1.09 [0.92; 1.30]; 0.293[f]
Constipation					
CASTOR[b, c]	251	8.8 [4.2; 16.6] 120 (47.8)	247	6.2 [4.5; NC] 100 (40.5)	1.01 [0.77; 1.33]; 0.948
POLLUX[d, e]	286	4.7 [2.9; 7.0] 162 (56.6)	283	3.3 [2.0; 5.7] 165 (58.3)	0.87 [0.70; 1.08]; 0.214
Total					0.92 [0.78; 1.09]; 0.346[f]
Diarrhoea					
CASTOR[b, c]	251	5.7 [4.2; 9.1] 141 (56.2)	247	6.6 [4.9; 10.1] 98 (39.7)	1.16 [0.89; 1.52]; 0.284
POLLUX[d, e]	286	5.7 [4.7; 7.6] 195 (68.2)	283	5.7 [4.6; 7.7] 190 (67.1)	0.90 [0.73; 1.11]; 0.332
Total					0.99 [0.84; 1.17]; 0.916[f]

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: daratumumab arm vs. comparator arm (multipage table)

Outcome category outcome study	Daratumumab arm N	Daratumumab arm median time to event in months [95% CI] patients with event n (%)	Comparator arm N	Comparator arm median time to event in months [95% CI] patients with event n (%)	Daratumumab arm vs. comparator arm HR [95% CI]; p-value[a]
Health-related quality of life					
EORTC QLQ-C30[i]					
Global health status					
CASTOR[b, c]	251	3.5 [2.8; 6.1] 139 (55.4)	247	4.0 [2.9; 5.1] 118 (47.8)	0.97 [0.76; 1.25]; 0.831
POLLUX[d, e]	286	4.7 [2.9; 7.4] 169 (59.1)	283	4.7 [2.9; 7.5] 169 (59.7)	0.92 [0.74; 1.15]; 0.463
Total					0.94 [0.80; 1.11]; 0.475[f]
Physical functioning					
CASTOR[b, c]	251	4.4 [3.6; 5.7] 154 (61.4)	247	4.3 [3.5; 5.9] 119 (48.2)	0.98 [0.76; 1.26]; 0.889
POLLUX[d, e]	286	6.0 [4.0; 8.6] 169 (59.1)	283	7.5 [5.6; 10.2] 162 (57.2)	1.01 [0.81; 1.26]; 0.909
Total					1.00 [0.84; 1.18]; 0.971[f]
Role functioning					
CASTOR[b, c]	251	2.3 [1.6; 2.9] 165 (65.7)	247	2.8 [2.1; 3.8] 131 (53.0)	1.18 [0.93; 1.49]; 0.174
POLLUX[d, e]	286	3.7 [2.8; 4.7] 195 (68.2)	283	3.1 [2.8; 4.7] 186 (65.7)	0.97 [0.79; 1.19]; 0.770
Total					1.06 [0.90; 1.23]; 0.495[f]
Emotional functioning					
CASTOR[b, c]	251	6.0 [4.5; 10.5] 131 (52.2)	247	4.9 [3.5; 7.1] 110 (44.5)	0.83 [0.64; 1.08]; 0.169
POLLUX[d, e]	286	6.6 [4.7; 11.4] 150 (52.4)	283	8.4 [4.9; 13.0] 143 (50.5)	1.04 [0.82; 1.31]; 0.768
Total					0.94 [0.79; 1.12]; 0.492[f]
Cognitive functioning					
CASTOR[b, c]	251	3.5 [2.8; 4.2] 152 (60.6)	247	3.5 [2.3; 4.9] 124 (50.2)	0.95 [0.74; 1.21]; 0.671
POLLUX[d, e]	286	4.9 [3.8; 7.4] 192 (67.1)	283	4.7 [3.1; 6.6] 174 (61.5)	0.96 [0.78; 1.19]; 0.703
Total					0.96 [0.81; 1.12]; 0.580[f]

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: daratumumab arm vs. comparator arm (multipage table)

Outcome category outcome study	Daratumumab arm N	Daratumumab arm median time to event in months [95% CI] patients with event n (%)	Comparator arm N	Comparator arm median time to event in months [95% CI] patients with event n (%)	Daratumumab arm vs. comparator arm HR [95% CI]; p-value[a]
Social functioning					
CASTOR[b, c]	251	2.9 [2.2; 3.6] 171 (68.1)	247	3.0 [2.2; 4.2] 130 (52.6)	1.12 [0.88; 1.42]; 0.352
POLLUX[d, e]	286	3.8 [3.0; 6.5] 181 (63.3)	283	2.9 [2.0; 4.6] 190 (67.1)	0.80 [0.65; 0.99]; 0.038
Total					0.93 [0.79; 1.08]; 0.343[f]
Side effects					
AEs (supplementary information)					
CASTOR[b, c]	243	0.03 [0.03; 0.10] 241 (99.2)	237	0.3 [0.3; 0.5] 226 (95.4)	–
POLLUX[d, e]	283	0.03 [NC]; 282 (99.6)	281	0.2 [0.1; 0.3] 274 (97.5)	–
SAEs					
CASTOR[b, c]	243	14.4 [6.7; 29.0] 134 (55.1)	237	NA 81 (34.2)	1.31 [0.98; 1.76]; 0.071
POLLUX[d, e]	283	14.3 [9.7; 17.5] 205 (72.4)	281	15.6 [11.8; 23.2] 148 (52.7)	1.08 [0.87; 1.35]; 0.468
Total					1.16 [0.97; 1.38]; 0.102[f]
Severe AEs[j]					
CASTOR[b, c]	243	1.2 [0.9; 1.2] 201(82.7)	237	1.8 [1.2; 3.5] 151 (63.7)	1.40 [1.13; 1.75]; 0.002
POLLUX[d, e]	283	1.0 [0.7; 1.4] 262 (92.6)	281	3.4 [2.3; 4.7] 231 (82.2)	1.37 [1.14; 1.65]; < 0.001
Total					1.38 [1.20; 1.59];< 0.001[f]
Discontinuation due to AEs (at least one drug component)					
CASTOR[b, c]	243	NA 45 (18.5)	237	NA 39 (16.5)	0.88 [0.56; 1.38]; 0.563
POLLUX[d, e]	283	65.0 [51.0; NC] 111 (39.2)	281	58.2 [47.7; NC] 74 (26.3)	0.92 [0.68; 1.25]; 0.602
Total					0.91 [0.70; 1.17]; 0.450[f]
Specific AEs					
Infusion related reaction					
CASTOR[b, c]		Analysis not suitable[k]			
POLLUX[d, e]					

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: daratumumab arm vs. comparator arm (multipage table)

Outcome category outcome study	Daratumumab arm N	Daratumumab arm median time to event in months [95% CI] patients with event n (%)	Comparator arm N	Comparator arm median time to event in months [95% CI] patients with event n (%)	Daratumumab arm vs. comparator arm HR [95% CI]; p-value[a]
Peripheral neuropathy NRE (HLT, severe AEs)[l]					
CASTOR[b, c]	243	NA 14 (5.8)	237	NA 17 (7.2)	0.67 [0.32; 1.38]; 0.276
Vomiting (PT, AEs)					
CASTOR[b, c]	243	NA 30 (12.3)	237	NA 9 (3.8)	2.89 [1.35; 6.18]; 0.006
POLLUX[d, e]	283	NA 66 (23.3)	281	NA 20 (7.1)	2.94 [1.77; 4.88]; < 0.001
Total					2.92 [1.92; 4.46]; < 0.001[f, m]
Blood and lymphatic system disorders (SOC, severe AEs)					
CASTOR[b, c]	243	1.9 [1.2; 14.8] 137 (56.4)	237	NA 95 (40.1)	1.62 [1.24; 2.12]; < 0.001
POLLUX[d, e]	283	3.5 [1.6; 8.9] 184 (65.0)	281	9.9 [6.7; 14.9] 163 (58.0)	1.21 [0.98; 1.51]; 0.080
Total					1.36 [1.15; 1.61]; < 0.001[f, m]
Respiratory, thoracic and mediastinal disorders (SOC, severe AEs)					
CASTOR[b, c]	243	NA 36 (14.8)	237	NA 12 (5.1)	2.36 [1.20; 4.64]; 0.013
POLLUX[d, e]	283	NA 43 (15.2)	281	NA 24 (8.5)	1.28 [0.76; 2.15]; 0.354
Total					1.61 [1.06; 2.43]; 0.024[f, m]
Diarrhoea (PT, severe AEs)					
CASTOR[b, c]	243	NA 10 (4.1)	237	NA 3 (1.3)	3.00 [0.81; 11.14]; 0.101
POLLUX[d, e]	283	NA 29 (10.2)	281	NA 11 (3.9)	1.83 [0.90; 3.72]; 0.096
Total					2.05 [1.10; 3.82]; 0.024[f, m]
Hypertension (PT, severe AEs)					
CASTOR[b, c]	243	NA 18 (7.4)	237	NA 2 (0.8)	7.01 [1.60; 30.71]; 0.010
POLLUX[d, e]	283	NA 13 (4.6)	281	NA 5 (1.8)	1.82 [0.64; 5.20]; 0.266
Total					2.86 [1.22; 6.72]; 0.016[f, m]

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: daratumumab arm vs. comparator arm (multipage table)

Outcome category outcome study	Daratumumab arm		Comparator arm		Daratumumab arm vs. comparator arm
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value[a]
a. Cox proportional hazards model stratified by ISS stage (I vs. II vs. III), number of prior therapies (1 vs. 2 or 3 vs. ≥ 4) and prior treatment with bortezomib (CASTOR)/lenalidomide (POLLUX) (no vs. yes). b. The CASTOR study compared daratumumab + bortezomib + dexamethasone with bortezomib + dexamethasone. c. Data cut-off 28 June 2021. d. The POLLUX study compared daratumumab + lenalidomide + dexamethasone with lenalidomide + dexamethasone. e. Data cut-off 30 September 2021. f. calculated from meta-analysis (fixed-effect model). g. Time to first deterioration. A decrease of the score by ≥ 15 points from baseline is considered a clinically relevant deterioration (scale range 0 to 100). h. Time to first deterioration. An increase of the score by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range 0 to 100). i. Time to first deterioration. A decrease of the score by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range 0 to 100). j. Operationalized as CTCAE grade ≥ 3. k. The analysis presented by the company is not suitable for the benefit assessment; however, the events underlying the outcome are additionally recorded via the specific AEs. See Section 2.4.1 for reasons. l. This AE is specific for the drug bortezomib and thus irrelevant for the POLLUX study. m. Institute's calculation. AE: adverse event; NRE: not recorded elsewhere; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HLT: High Level Term; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; NC: not calculable; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale					

Based on the available information, at most proofs, e.g. of an added benefit, can be determined for the outcomes “overall survival” and “severe AEs”, and at most indications can be determined for all other outcomes due to the high risk of bias.

Mortality

Overall survival

The meta-analysis of the studies CASTOR and POLLUX showed a statistically significant difference in favour of daratumumab between the treatment groups for the outcome "overall survival". As a result, there was proof of an added benefit of daratumumab in comparison with the ACT.

Morbidity

Health status (EQ-5D VAS)

For the outcome "health status", the meta-analysis of the studies CASTOR and POLLUX does not show any statistically significant difference between the treatment groups. This resulted in no hint of an added benefit of daratumumab in comparison with the ACT for the outcome "health status"; an added benefit is therefore not proven.

Symptoms (EORTC QLQ-C30)

Symptom outcomes were recorded using the EORTC QLQ-C30 symptom scales. The meta-analysis of the studies CASTOR and POLLUX showed no statistically significant difference between the treatment groups for each of the following outcomes: fatigue, nausea and vomiting, pain, dyspnoea, insomnia, loss of appetite, constipation and diarrhoea. This resulted in no hint of an added benefit of daratumumab in comparison with the ACT for these outcomes; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

Outcomes on health-related quality of life were recorded with the EORTC QLQ-C30 functional scales. The meta-analysis of the studies CASTOR and POLLUX showed no statistically significant difference between the treatment groups for each of the following outcomes: global health status, physical functioning, role functioning, emotional functioning, and cognitive functioning. This resulted in no hint of an added benefit of daratumumab in comparison with the ACT for these outcomes; an added benefit is therefore not proven.

For the outcome "social functioning", the meta-analysis of the studies CASTOR and POLLUX shows no statistically significant difference between the treatment groups, but there is an effect modification by the characteristic "age" (see Section 2.4.4). This results in an indication of an added benefit of daratumumab versus the ACT for patients ≥ 65 years of age. For patients < 65 years, there was no hint of an added benefit of daratumumab versus the ACT; an added benefit is therefore not proven for these patients.

Side effects

SAEs

For the outcome "SAEs", the meta-analysis of the studies CASTOR and POLLUX does not show any statistically significant difference between the treatment arms. For the outcome "SAEs", there was no hint of greater or lesser harm from daratumumab in comparison with the ACT; greater or lesser harm is therefore not proven.

Severe AEs

The meta-analysis of the studies CASTOR and POLLUX showed a statistically significant difference to the disadvantage of daratumumab in comparison with the ACT for the outcome "severe AEs". For both studies, high certainty of results was assumed despite the high risk of

bias (see Section 2.4.2). However, there was an effect modification by the characteristic of ISS stage (see Section 2.4.4). This resulted in a proof of greater harm from daratumumab versus the ACT for patients with ISS stage I. For patients in ISS stages II and III, there is no hint of greater or lesser harm from daratumumab versus the ACT; greater or lesser harm is arm is therefore not proven for these patients.

Discontinuation due to AEs (at least one drug component)

The meta-analysis showed no statistically significant difference between the treatment arms for the outcome "discontinuation due to AEs (at least one drug component)". This resulted in no hint of greater or lesser harm from daratumumab in comparison with the ACT for the outcome “discontinuation due to AEs”; greater or lesser harm is therefore not proven.

Infusion related reactions

The analyses presented by the company for the outcome “infusion related reaction” are not suitable for the benefit assessment (see Section 2.4.1). However, the events on which infusion-related reactions are based are covered by the specific AEs.

This resulted in no hint of greater or lesser harm from daratumumab in comparison with the ACT; greater or lesser harm is therefore not proven.

Peripheral neuropathy NRE (HLT, severe AEs)

As a specific AE of bortezomib, the outcome “peripheral neuropathy NRE (HLT, severe AEs)” is of particular interest only for patients treated with bortezomib. There was no statistically significant difference between the treatment arms in the CASTOR study. This resulted in no hint of greater or lesser harm from daratumumab + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone for this outcome; greater or lesser harm is therefore not proven.

Specific AEs

Vomiting (PT, AEs), blood and lymphatic system disorders (SOC, severe AEs), respiratory, thoracic and mediastinal disorders (SOC, severe AEs), diarrhoea (PT, severe AEs), hypertension (PT, severe AEs)

The meta-analysis of the studies CASTOR and POLLUX shows a statistically significant difference to the disadvantage of daratumumab versus the ACT for each of the following outcomes: vomiting (PT, AEs), blood and lymphatic system disorders (SOC, severe AEs), respiratory, thoracic and mediastinal disorders (SOC, severe AEs), diarrhoea (PT, severe AEs) and hypertension (PT, severe AEs). This results in an indication of greater harm from daratumumab in comparison with the ACT for each of these 5 specific AEs.

2.4.4 Subgroups and other effect modifiers

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

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

The mentioned characteristics were defined a priori. The company did not present interaction tests based on meta-analyses of the studies POLLUX and CASTOR in its dossier. These were therefore calculated by the Institute.

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

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

In its dossier, the company did not present any interaction tests based on meta-analyses of the studies POLLUX and CASTOR for the specific AEs considered in the present benefit assessment. Due to missing information for individual SOCs/PTs, these can also not be fully calculated. Subgroup results for specific AEs could therefore not be used for the present assessment.

The results are presented in Table 16. No Kaplan-Meier curves are available on the subgroup results for the outcome “severe AEs”. Kaplan-Meier curves on the subgroup results for the outcome “social functioning” are only available for the CASTOR study; they are presented in Appendix D of the full dossier assessment.

Table 16: Subgroups (health-related quality of life, side effects) – RCT, direct comparison: daratumumab arm vs. comparator arm (multipage table)

Outcome characteristic study subgroup	Daratumumab arm N	Daratumumab arm median time to event in months [95 % CI] patients with event n (%)	Comparator arm N	Comparator arm median time to event in months [95 % CI] patients with event n (%)	Daratumumab arm vs. comparator arm HR [95% CI]	Daratumumab arm vs. comparator arm p-value
Health-related quality of life (EORTC QLQ-C30)[a]						
Social functioning						
Age						
CASTOR						
< 65 years	132	2.9 [1.8; 4.2] 89 (67.4)	125	5.2 [2.9; NC] 54 (43.2)	1.43 [1.01; 2.01][b]	0.043[b]
≥ 65 years	119	3.0 [2.1; 4.0] 82 (68.9)	122	2.2 [1.5; 3.0] 76 (62.3)	0.84 [0.61; 1.17][b]	0.306[b]
POLLUX						
< 65 years	133	4.6 [3.1; 7.5] 87 (65.4)	140	3.8 [2.8; 4.8] 89 (63.6)	0.91 [0.67; 1.22][b]	0.508[b]
≥ 65 years	153	3.3 [2.1; 8.4] 94 (61.4)	143	1.9 [1.9; 3.0] 101 (70.6)	0.73 [0.55; 0.97][b]	0.028[b]
Total					Interaction:	0.025[c]
< 65 years					1.11 [0.88; 1.39][d]	0.383[d]
≥ 65 years					0.78 [0.63; 0.96][d]	0.020[d]
Severe AEs (CTCAE grade ≥ 3)						
ISS stage						
CASTOR						
Stage I	98	1.4 [1.1; 3.0] 79 (80.6)	92	5.4 [2.1; NC] 45 (48.9)	1.77 [1.22; 2.58][b]	0.003[b]
Stage II	92	1.2 [0.7; 1.9] 76 (82.6)	97	1.3 [1.1; 2.9] 70 (72.2)	1.13 [0.81; 1.58][b]	0.462[b]
Stage III	53	0.5 [0.3; 0.7] 46 (86.8)	48	0.7 [0.5; 1.7] 36 (75.0)	1.39 [0.89; 2.15][b]	0.148[b]
POLLUX						
Stage I	136	0.8 [0.7; 1.8] 123 (90.4)	139	7.1 [3.7; 9.9] 107 (77.0)	1.66 [1.28; 2.16][b]	< 0.001[b]
Stage II	93	1.4 [0.7; 2.7] 89 (95.7)	86	2.4 [1.5; 3.8] 74 (86.0)	1.05 [0.77; 1.44][b]	0.759[b]
Stage III	54	0.7 [0.7; 1.1] 50 (92.6)	56	1.2 [0.5; 2.3] 50 (89.3)	1.20 [0.81; 1.78][b]	0.369[b]
Total					Interaction:	0.019[c]
Stage I					1.70 [1.37; 2.10][d]	< 0.001[d]
Stage II					1.09 [0.86; 1.37][d]	0.476[d]
Stage III					1.28 [0.95; 1.72][d]	0.099[d]

Table 16: Subgroups (health-related quality of life, side effects) – RCT, direct comparison: daratumumab arm vs. comparator arm (multipage table)

Outcome characteristic study subgroup	Daratumumab arm N	Daratumumab arm median time to event in months [95 % CI] patients with event n (%)	Comparator arm N	Comparator arm median time to event in months [95 % CI] patients with event n (%)	Daratumumab arm vs. comparator arm HR [95% CI]	Daratumumab arm vs. comparator arm p-value
a. Time to first deterioration. A decrease of the score by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range 0 to 100). b. Cox proportional hazards model. c. Institute's calculation, Cochran's Q test. d. Institute's calculation; meta-analysis with fixed effect. AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; ISS: International Staging System; N: number of analysed patients; n: number of patients with (at least one) event; QLQ-C30: Quality of Life Questionnaire Core-30; RCT: randomized controlled trial						

Health-related quality of life

EORTC QLQ-C30

Social functioning

There was an effect modification by the characteristic "age" for the outcome "social functioning".

A statistically significant difference in favour of daratumumab in comparison with the ACT was shown for patients with≥ 65 years at study inclusion. This resulted in an indication of an added benefit of daratumumab in comparison with the ACT.

For patients < 65 years at study inclusion, in contrast, there was no statistically significant difference between treatment groups. This resulted in no hint of an added benefit of daratumumab in comparison with the ACT; an added benefit is therefore not proven.

Side effects

Severe AEs (CTCAE grade ≥ 3)

There was an effect modification by the characteristic “ISS stage” for the outcome “severe AEs (CTCAE grade ≥ 3)”.

A statistically significant effect to the disadvantage of daratumumab in comparison with the ACT was shown for patients with ISS stage I. This resulted in a proof of greater harm from daratumumab in comparison with the ACT for these patients.

However, there was no statistically significant difference between the treatment groups for patients with ISS stages II and III. This resulted in no hint of greater or lesser harm from

daratumumab in comparison with the ACT; greater or lesser harm is therefore not proven for these patients.

2.5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [39].

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

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.4 (see Table 17).

Table 17: Extent of added benefit at outcome level: daratumumab arm versus comparator arm (multipage table)

Outcome category outcome	**Daratumumab arm vs. comparator arm median time to event (months) effect estimation [95% CI]; p-value probability[a]**	**Derivation of extent[b]**
Total observation period		
Mortality		
Overall survival	49.6-67.6 vs. 38.5-51.8[c] HR: 0.74 [0.63; 0.86] p < 0.001 probability: "proof"	Outcome category: mortality $0.85 \leq CI_u < 0.95$ added benefit, extent: “considerable”
Shortened observation period		
Morbidity		
Health status (EQ-5D VAS (deterioration by ≥ 15 points)		
EQ-5D VAS	10.1-11.2 vs. 6.4-11.6[c] HR: 0.96 [0.80; 1.15] p = 0.647	Lesser benefit/added benefit not proven
Symptoms (EORTC QLQ-C30, deterioration ≥ 10 points)		
Fatigue	1.5-1.9 vs. 2.0-2.1[c] HR: 1.09 [0.94; 1.26] p = 0.266	Lesser benefit/added benefit not proven
Nausea and vomiting	6.8–13.0 vs. 10.2-NA[c] HR: 1.04 [0.87; 1.25] p = 0.677	Lesser benefit/added benefit not proven
Pain	3.5-5.6 vs. 3.6-5.6[c] HR: 0.95 [0.81; 1.12] p = 0.566	Lesser benefit/added benefit not proven
Dyspnoea	3.6-4.7 vs. 2.9-5.7[c] HR: 0.98 [0.83; 1.15] p = 0.766	Lesser benefit/added benefit not proven
Insomnia	2.4-6.6 vs. 2.9-3.8[c] HR: 0.93 [0.79; 1.09] p = 0.367	Lesser benefit/added benefit not proven
Appetite loss	5.0-7.2 vs. 6.0-9.6[c] HR: 1.09 [0.92; 1.30] p = 0.293	Lesser benefit/added benefit not proven
Constipation	4.7-8.8 vs. 3.3-6.2[c] HR: 0.92 [0.78; 1.09] p = 0.346	Lesser benefit/added benefit not proven
Diarrhoea	5.7 vs. 5.7-6.6[c] HR: 0.99 [0.84; 1.17] p = 0.916	Lesser benefit/added benefit not proven

Table 17: Extent of added benefit at outcome level: daratumumab arm versus comparator arm (multipage table)

Outcome category **outcome**	**Daratumumab arm vs. comparator arm** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability[a]**	**Derivation of extent[b]**
Health-related quality of life **(EORTC QLQ-C30, deterioration ≥ 10 points)**		
Global health status	3.5-4.7 vs. 4.0-4.7[c] HR: 0.94 [0.80; 1.11] p = 0.475	Lesser benefit/added benefit not proven
Physical functioning	4.4-6.0 vs. 4.3-7.5[c] HR: 1.00 [0.84; 1.18] p = 0.971	Lesser benefit/added benefit not proven
Role functioning	2.3-3.7 vs. 2.8-3.1[c] HR: 1.06 [0.90; 1.23] p = 0.495	Lesser benefit/added benefit not proven
Emotional functioning	6.0-6.6 vs. 4.9-8.4[c] HR: 0.94 [0.79; 1.12] p = 0.492	Lesser benefit/added benefit not proven
Cognitive functioning	3.5-4.9 vs. 3.5-4.7[c] HR: 0.96 [0.81; 1.12] p = 0.580	Lesser benefit/added benefit not proven
Social functioning		
Age		
< 65 years	2.9-4.6 vs. 3.8-5.2[c] HR: 1.11 [0.88; 1.39] p = 0.383	Lesser benefit/added benefit not proven
≥ 65 years	3.0-3.3 vs. 1.9-2.2[c] HR: 0.78 [0.63; 0.96] p = 0.020 probability: "indication"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: “minor”

Table 17: Extent of added benefit at outcome level: daratumumab arm versus comparator arm (multipage table)

Outcome category outcome	**Daratumumab arm vs. comparator arm median time to event (months) effect estimation [95% CI]; p-value probability[a]**	**Derivation of extent[b]**
Side effects		
SAEs	14.3–14.4 vs. 15.6-NA[c] HR: 1.16 [0.97; 1.38] p = 0.102	Greater/lesser harm not proven
Severe AEs		
ISS stage		
Stage I	0.8-1.4 vs. 5.4-7.1[c] HR: 1.70 [1.37; 2.10] HR: 0.59 [0.48; 0.73][d] p < 0.001 probability: "proof"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% greater harm, extent: “major”
Stage II	1.2-1.4 vs. 1.3-2.4[c] HR: 1.09 [0.86; 1.37] p = 0.476	Greater/lesser harm not proven
Stage III	0.5-0.7 vs. 0.7-1.2[c] HR: 1.28 [0.95; 1.72] p = 0.099	Greater/lesser harm not proven
Discontinuation due to AEs (at least one drug component)	65.0–NA vs. 58.2-NA[c] HR: 0.91 [0.70; 1.17] p = 0.450	Greater/lesser harm not proven
Infusion related reactions	Analysis not suitable[e]	Greater/lesser harm not proven
Peripheral neuropathy (severe AE)	NA vs. NA HR: 0.67 [0.32; 1.38][f] p = 0.276	Greater/lesser harm not proven
Vomiting (AE)	NA vs. NA[c] HR: 2.92 [1.92; 4.46] HR: 0.34 [0.22; 0.52][d] p < 0.001 probability: "indication”	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: “considerable”
Blood and lymphatic system disorders (severe AEs)	1.9–3.5 vs. 9.9-NA[c] HR: 1.36 [1.15; 1.61] HR: 0.74 [0.62; 0.87][d] p < 0.001 probability: "indication”	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: “considerable”
Respiratory, thoracic and mediastinal disorders (severe AE)	NA vs. NA[c] HR: 1.61 [1.06; 2.43] HR: 0.62 [0.41; 0.94][d] p = 0.024 probability: "indication”	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: “minor”

Table 17: Extent of added benefit at outcome level: daratumumab arm versus comparator arm (multipage table)

Outcome category **outcome**	**Daratumumab arm vs. comparator arm** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Diarrhoea (severe AE)	NA vs. NA[c] HR: 2.05 [1.10; 3.82] HR: 0.49 [0.26; 0.91][d] p = 0.024 probability: "indication"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: "minor"
Hypertension (severe AE)	NA vs. NA[c] HR: 2.86 [1.22; 6.72] HR: 0.35 [0.15; 0.82][d] p = 0.016 probability: "indication"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"

a. Probability provided if statistically significant differences are present.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Minimum and maximum medians of the time to event in each treatment arm in the studies included.
d. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
e. The analysis presented by the company is not suitable for the benefit assessment; however, the events underlying the outcome are additionally recorded via the specific AEs. See Section 2.4.1 for reasons.
f. The result is based on only one study.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; ISS: International Staging System; QLQ-C30: Quality of Life Questionnaire – Core 30; SAE: serious adverse event; VAS: visual analogue scale

2.5.2 Overall conclusion on added benefit

Table 18 summarizes the results included in the overall conclusion on the extent of added benefit.

Table 18: Positive and negative effects from the assessment of daratumumab in comparison with the ACT

Positive effects	Negative effects
Total observation period	
Mortality ▪ overall survival: proof of an added benefit – extent "considerable"	–
Shortened observation period	
Health-related quality of life ▪ social functioning (EORTC QLQ-C30) ▫ age (≥ 65 years): indication of added benefit – extent: “minor”	–
–	Serious/severe side effects ▪ severe AEs: ▫ ISS stage (stage I): Proof of greater harm – extent: “major” ▪ blood and lymphatic system disorders (severe AE): indication of greater harm – extent "considerable" ▪ respiratory, thoracic and mediastinal disorders (severe AE): indication of greater harm – extent: “minor” ▪ diarrhoea (severe AE): indication of greater harm – extent: “minor” ▪ hypertension (severe AE): indication of greater harm – extent "considerable"
–	Non-serious/non-severe side effects ▪ vomiting (AE): indication of greater harm – extent: "considerable"
There are no usable data from the LEPUS study, because the results on patient-relevant outcomes are incomplete.	
AE: adverse event; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30	

The overall assessment shows both positive and negative effects with different extents for daratumumab compared with the ACT.

On the side of the positive effects, there is proof of an added benefit with the extent “considerable” for the outcome “overall survival”. For patients ≥ 65 years, there is also an indication of minor added benefit in the outcome “social functioning”.

The negative effects exclusively refer to outcomes in the category of AEs: the total rate of severe AEs with the extent “major” for patients in ISS stage I, as well as 5 specific AEs, some with the extent “considerable”, some with the extent “minor” for the total population. There is proof of greater harm for “severe AEs”; indications of greater harm were derived for each of the specific AEs. The negative effects refer exclusively to the shortened period until the end of treatment (plus a maximum of 30 days).

The effects described are based on the results of the studies CASTOR and POLLUX; the LEPUS study provided no usable data.

Thus, a positive effect in the outcome "overall survival" with the extent "considerable" is offset by negative effects in the outcome category of side effects, of which the total rate of severe AEs with the extent "major" is of particular importance for patients in ISS stage I due to the high certainty of conclusions. Regarding magnitude and certainty of conclusions, the advantage in the outcome "social functioning" for patients ≥ 65 years is secondary to the advantage in overall survival for the total population and therefore does not influence the overall assessment. The negative effects do not completely challenge the positive effect for the outcome "overall survival"; however, in the overall consideration, they influence the extent of the added benefit. This is regarded as considerable for patients in ISS stages II and III, and as minor for patients in ISS stage I due to the disadvantage in the outcome "severe AEs".

It is assumed that the results of the LEPUS study do not challenge this overall assessment (see Section 2.4.1).

In summary, there is proof of considerable added benefit of daratumumab versus the ACT for adults with ISS stage II or III multiple myeloma who have received at least one prior therapy, and proof of minor added benefit of daratumumab versus the ACT for adults with ISS stage I multiple myeloma who have received at least one prior therapy.

Table 19 summarizes the result of the assessment of the added benefit of daratumumab in comparison with the ACT.

Table 19: Daratumumab – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adult patients with multiple myeloma who have received at least one prior therapy[b, c]	Bortezomib in combination with pegylated liposomal doxorubicin or bortezomib in combination with dexamethasone or lenalidomide in combination with dexamethasone or elotuzumab in combination with lenalidomide and dexamethasone or carfilzomib in combination with lenalidomide and dexamethasone or carfilzomib in combination with dexamethasone	Patients with ISS stage II or III: ▪ proof of considerable added benefit
		Patients with ISS stage I: ▪ proof of minor added benefit

a. Presented is the ACT specified by the G-BA. The company did not restrict the inclusion criteria for the search for studies relevant to the assessment with regard to the drugs, but included all drugs named by the G-BA.
b. It is assumed that high-dose chemotherapy with stem cell transplantation was not an option for the patients at the time point of their current treatment.
c. It is assumed that the special situation of refractory patients will be taken into account when choosing the ACT.

G-BA: Federal Joint Committee

The assessment described above deviates from that of the company, which derived proof of considerable added benefit for all patients regardless of the ISS stage.

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

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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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