

Daratumumab (newly diagnosed multiple myeloma, ineligible for stem cell transplant)

Benefit assessment according to §35a SGB V¹

EXTRACT

Project: A25-108 Version: 1.0 Status: 13 Nov 2025 DOI: 10.60584/A25-108_en

¹ Translation of Sections I 1 to I 6 of the dossier assessment *Daratumumab (neu diagnostiziertes multiples Myelom, Stammzelltransplantation nicht geeignet) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Daratumumab (newly diagnosed multiple myeloma, ineligible for stem cell transplant) –
Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

18 August 2025

Internal Project No.

A25-108

DOI-URL

https://doi.org/10.60584/A25-108_en

Address of publisher

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Siegburger Str. 237
50679 Köln
Germany

Phone: +49 221 35685-0

Fax: +49 221 35685-1

Email: berichte@iqwig.de

Internet: www.iqwig.de

Recommended citation

Institute for Quality and Efficiency in Health Care. Daratumumab (newly diagnosed multiple myeloma, ineligible for stem cell transplant); Benefit assessment according to §35a SGB V; Extract [online]. 2025 [Accessed: DD.MM.YYYY]. URL: https://doi.org/10.60584/A25-108_en.

Keywords

Daratumumab, Bortezomib, Lenalidomide, Dexamethasone, Multiple Myeloma, Benefit Assessment, NCT03652064

Medical and scientific advice

- Jochem Potenberg, Waldkrankenhaus Protestant Hospital, Berlin, Germany

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

Patient and family involvement

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

IQWiG thanks the respondent and the patient organization 'Plasmozytom/Multiples Myelom NRW' for participating in the written exchange and for their support. The respondent and 'Plasmozytom/Multiples Myelom NRW' were not involved in the actual preparation of the dossier assessment.

IQWiG employees involved in the dossier assessment

- Marina Goddon
- Ivona Djuric
- Stefan Kobza
- Philip Kranz
- Prateek Mishra
- Mattea Patt
- Felix Schwarz
- Dorothea Sow
- Carolin Weigel

Part I: Benefit assessment

I Table of contents

	Page
I List of tables	I.3
I List of abbreviations.....	I.5
I 1 Executive summary of the benefit assessment	I.1
I 2 Research question.....	I.10
I 3 Information retrieval and study pool.....	I.12
I 3.1 Studies included	I.12
I 3.2 Study characteristics	I.13
I 4 Results on added benefit.....	I.33
I 4.1 Outcomes included	I.33
I 4.2 Risk of bias	I.35
I 4.3 Results.....	I.37
I 4.4 Subgroups and other effect modifiers	I.42
I 5 Probability and extent of added benefit	I.44
I 5.1 Assessment of added benefit at outcome level.....	I.44
I 5.2 Overall conclusion on added benefit	I.48
I 6 References for English extract	I.50

I List of tables²

	Page
Table 2: Research question of the benefit assessment of daratumumab + bortezomib + lenalidomide + dexamethasone	I.2
Table 3: Daratumumab + bortezomib + lenalidomide + dexamethasone – probability and extent of added benefit	I.9
Table 4: Research question for the benefit assessment of daratumumab + bortezomib + lenalidomide + dexamethasone	I.10
Table 5: Study pool – RCT, direct comparison: daratumumab + bortezomib + lenalidomide + dexamethasone vs. bortezomib + lenalidomide + dexamethasone	I.12
Table 6: Characteristics of the study included – RCT, direct comparison: daratumumab + bortezomib + lenalidomide + dexamethasone vs. bortezomib + lenalidomide + dexamethasone	I.14
Table 7: Characteristics of the intervention – RCT, direct comparison: daratumumab + bortezomib + lenalidomide + dexamethasone vs. bortezomib + lenalidomide + dexamethasone	I.16
Table 8: Planned duration of follow-up – RCT, direct comparison: daratumumab + bortezomib + lenalidomide + dexamethasone vs. bortezomib + lenalidomide + dexamethasone	I.22
Table 9: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: daratumumab + bortezomib + lenalidomide + dexamethasone vs. bortezomib + lenalidomide + dexamethasone, relevant subpopulation	I.23
Table 10: Information on the course of the study – RCT, direct comparison: daratumumab + bortezomib + lenalidomide + dexamethasone vs. bortezomib + lenalidomide + dexamethasone, relevant subpopulation	I.26
Table 11: Information on subsequent antineoplastic therapies (≥ 2 patients in both treatment arms combined) – RCT, direct comparison: daratumumab + bortezomib + lenalidomide + dexamethasone vs. bortezomib + lenalidomide + dexamethasone, relevant subpopulation	I.28
Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: daratumumab + bortezomib + lenalidomide + dexamethasone vs. bortezomib + lenalidomide + dexamethasone	I.31
Table 13: Matrix of outcomes – RCT, direct comparison: daratumumab + bortezomib + lenalidomide + dexamethasone vs. bortezomib + lenalidomide + dexamethasone	I.34
Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: daratumumab + bortezomib + lenalidomide + dexamethasone vs. bortezomib + lenalidomide + dexamethasone	I.36

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

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: daratumumab + bortezomib + lenalidomide + dexamethasone vs. bortezomib + lenalidomide + dexamethasone, relevant subpopulation	I.38
Table 16: Extent of added benefit at outcome level: daratumumab + bortezomib + lenalidomide + dexamethasone vs. bortezomib + lenalidomide + dexamethasone	I.45
Table 17: Positive and negative effects from the assessment of daratumumab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone	I.48
Table 18: Daratumumab + bortezomib + lenalidomide + dexamethasone – probability and extent of added benefit	I.49

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ASCT	autologous stem cell transplant
CD	cluster of differentiation
CTCAE	Common Terminology Criteria for Adverse Events
DGHO	Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (German Society for Haematology and Medical Oncology)
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
EHA	European Hematology Association
EMA	European Medicines Agency
EMN	European Myeloma Network
EORTC	European Organisation for Research and Treatment of Cancer
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HLT	High Level Term
IMWG	International Myeloma Working Group
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ISS	International Staging System
ITT	intention to treat
MMRM	mixed-effects model with repeated measures
MRD	minimal residual disease
PFS	progression-free survival
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-MY20	Quality of Life Questionnaire-Multiple Myeloma 20
RCT	randomized controlled trial
SAE	serious adverse event
SAP	statistical analysis plan
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	summary of product characteristics
VAS	visual analogue scale

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug daratumumab (in combination with bortezomib, lenalidomide and 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 18 August 2025.

Research question

The aim of this report is to assess the added benefit of daratumumab in combination with bortezomib, lenalidomide and dexamethasone (hereinafter 'daratumumab + bortezomib + lenalidomide + dexamethasone') in comparison with the appropriate comparator therapy (ACT) in adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (ASCT).

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of daratumumab + bortezomib + lenalidomide + dexamethasone

Therapeutic indication	ACT ^a
Adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant	▪ daratumumab in combination with lenalidomide and dexamethasone - or ▪ daratumumab in combination with bortezomib, melphalan and prednisone - or ▪ bortezomib in combination with melphalan and prednisone - or ▪ bortezomib in combination with lenalidomide and dexamethasone - or ▪ thalidomide in combination with melphalan and prednisone - or ▪ bortezomib in combination with cyclophosphamide and dexamethasone (only for patients with peripheral polyneuropathy or an increased risk of developing peripheral polyneuropathy^b)
a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company according to the inclusion criteria in Module 4 Section 4.2.2 is printed in bold. b. See Appendix VI to Section K of the Pharmaceutical Directive. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA's ACT and named all treatment options in Module 3 A and Module 4 A, but did not consider the option 'daratumumab in combination with bortezomib, melphalan and prednisone' in the inclusion criteria. The company did not justify its approach in the dossier, but presented data for the comparison with bortezomib in combination with lenalidomide and dexamethasone (hereinafter 'bortezomib + lenalidomide + dexamethasone'). The company's approach had no consequences for this benefit assessment, as no additional relevant study was identified in the review of the completeness of the study pool.

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

Study pool and study design

The study pool for this benefit assessment consists of the CEPHEUS study. However, there were uncertainties regarding the unsuitability of ASCT for the patients included (see below).

CEPHEUS

The CEPHEUS study is an ongoing, open-label RCT comparing daratumumab + bortezomib + lenalidomide + dexamethasone versus bortezomib + lenalidomide + dexamethasone.

It included patients ≥ 18 years of age with newly diagnosed multiple myeloma who are not candidates for high-dose chemotherapy with subsequent ASCT or who are candidates for high-dose therapy with subsequent ASCT but who refused this treatment. According to the inclusion criteria, patients were not candidates for high-dose chemotherapy with subsequent ASCT due to age ≥ 65 years, or age < 65 years with presence of relevant comorbid conditions. An inclusion due to refusal to have high-dose therapy with subsequent ASCT was therefore only possible for patients < 65 years without relevant comorbidities. In addition, the patients' general health at enrolment had to correspond to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 2. A total of 395 patients were randomized to the treatment arms: 197 to the intervention arm and 198 to the comparator arm.

The CEPHEUS study was divided into 2 treatment phases. In Cycles 1 to 8 (cycle length of 21 days), patients in the intervention arm were treated with daratumumab + bortezomib + lenalidomide + dexamethasone and in the comparator arm with bortezomib + lenalidomide + dexamethasone. Subsequently, in Cycle 9 and beyond (cycle length of 28 days), bortezomib was discontinued as part of the study medication in both treatment arms, and patients continued treatment with daratumumab + lenalidomide + dexamethasone or lenalidomide + dexamethasone.

Treatment in the intervention and comparator arm was carried out in compliance with the summaries of product characteristics (SmPCs). Treatment with the study medication was conducted until disease progression as per International Working Group (IMWG) criteria or unacceptable toxicity. If any component of the treatment regimen was discontinued, continued treatment with the remaining components was allowed.

The primary outcome in the CEPHEUS study was the minimal residual disease (MRD) negativity rate (based on a threshold of 10^{-5} malignant plasma cells in the bone marrow). Patient-relevant secondary outcomes included outcomes in the categories of mortality, morbidity, health-related quality of life and side effects.

Data cuts

The 3rd data cut of 7 May 2024 was used for the final analysis of progression-free survival (PFS).

Uncertainties regarding the CEPHEUS study – ASCT ineligibility of the study population questionable***Approach of the company***

According to the inclusion criteria of the CEPHEUS study, high-dose therapy with ASCT was not considered an option for patients who were at least 65 years of age, or who were younger than 65 years and had relevant comorbidities. In addition, patients younger than 65 years who were candidates for high-dose therapy with ASCT, but refused such treatment, were also included. According to the European Medicines Agency (EMA), patients who refuse ASCT, but who are eligible in principle, are not covered by this therapeutic indication. Furthermore, according to current guideline recommendations, the age criterion alone is not suitable for determining ineligibility for ASCT. Biological age in good general health is currently considered more important than chronological age when assessing eligibility for ASCT. It is difficult to define a maximum age for ASCT. Instead, individual patient factors should be considered when making treatment decisions, taking into account the patient's general condition, existing comorbidities, functional status and social integration. For the operationalization of ASCT ineligibility, it is therefore not appropriate to determine patient ineligibility for ASCT solely on the basis of age, as was done in the inclusion criteria of the CEPHEUS study for patients ≥ 65 years. However, in accordance with the electronic case report form (eCRF), the investigators also carried out an individual assessment of each patient's eligibility or ineligibility for ASCT for all patients under the age of 70 in the CEPHEUS study.

In Module 4 A, the company addressed the operationalization of ASCT ineligibility in the CEPHEUS study to represent the population under assessment, and presented post-hoc analyses for the 'ASCT ineligible' subpopulation as an approximation of a population ineligible for ASCT. This subpopulation included the following patients:

- Age < 70 years who are ineligible for ASCT according to the investigator's assessment
- Age ≥ 70 years

In the CEPHEUS study, 73% (289 of 395) of the patients included in the total population fulfilled these criteria.

In Module 4 A, the company also presented post hoc analyses of the subpopulation 'ASCT ineligible according to EMA criteria' in the form of subgroup analyses based on the subpopulation described above. The operationalization for ASCT ineligibility according to EMA criteria comprised the following patients:

- Age < 65 years with important comorbidities
- Age 65 to 69 years with ECOG PS = 2
- Age ≥ 70 years

These criteria were met by 79% (227 of 289) of the patients in the 'ASCT ineligible' subpopulation.

In Module 4 A, the company used the 'ASCT ineligible' subpopulation to derive the added benefit.

Assessment of the company's approach and consequences for the benefit assessment

The creation of the 'ASCT ineligible' subpopulation by excluding patients who are eligible for ASCT (27% of the total population, comprising patients who refused ASCT), and, based on this, the creation of the 'ASCT ineligible according to EMA criteria' subpopulation by the company, is understandable. This achieved an approximation to the research question population relevant to the benefit assessment. However, there were uncertainties in both subpopulations, which are described below.

In the CEPHEUS study, the investigators carried out an individual assessment of each patient's eligibility or ineligibility for ASCT for all patients under the age of 70. Such an individual assessment was therefore only carried out for 24% of the patients in the 'ASCT ineligible' subpopulation. The individual assessment was not carried out for patients aged ≥ 70 (76% of the 'ASCT ineligible' subpopulation) and it was not possible to determine the corresponding information post hoc. Hence there was the uncertainty that the exact proportion of patients in this subpopulation for whom ASCT would actually not have been suitable on an individual basis was unclear.

In addition to the 'ASCT ineligible' subpopulation, the company provided analyses of the 'ASCT ineligible according to EMA criteria' subpopulation in the form of subgroup analyses. In Module 4 A, the company described that the comparison of the patient characteristics and the analyses between the populations did not reveal any differences relevant for the benefit assessment. This assessment was appropriate. One reason for this was that the results between the 'ASCT ineligible' subpopulation and the 'ASCT ineligible according to EMA criteria' subpopulation were generally very similar for the decision-relevant outcomes. Another reason was that there were no consistent and relevant effect modifications by the characteristic 'ASCT ineligibility' / 'ASCT eligibility' (subgroups presented by the company: 'ASCT ineligible according to EMA criteria' versus 'ASCT eligible according to EMA criteria' [patients aged 65 to 69 years with an ECOG PS of 0 or 1]).

Since the difference between the 'ASCT ineligible' subpopulation and the 'ASCT ineligible according to EMA criteria' subpopulation was based solely on patients who received an individual assessment regarding ASCT ineligibility (65 to 69-year-olds with ECOG 0 to 1 in the 'ASCT ineligible' subpopulation), the 'ASCT ineligible' subpopulation was overall a better approximation to the target population. Since, in addition, comparable results were observed between the subpopulations, the results for the 'ASCT ineligible' subpopulation were used for

this benefit assessment, in an analogous manner to the approach used by the company. However, this subpopulation was still subject to uncertainty (see previous explanations). This uncertainty was taken into account in the certainty of conclusions.

Risk of bias

The risk of bias across outcomes was rated as low for the study. The risk of bias in the results for all outcomes was rated as high.

Summary assessment of the certainty of conclusions

Irrespective of the aspects described under the risk of bias, the certainty of conclusions of the study results was limited due to the uncertainties regarding ASCT ineligibility of the relevant subpopulation included. The results of the CEPHEUS study can therefore at most be used to derive hints, for example of an added benefit.

Results

Mortality

Overall survival

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

Morbidity

Symptoms (recorded with the EORTC QLQ-C30)

Fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, and diarrhoea

No statistically significant difference between the treatment arms was shown for any of the outcomes of fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, and diarrhoea. There was no hint of an added benefit of daratumumab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone for any of the outcomes; an added benefit is therefore not proven in each case.

Constipation

A statistically significant difference in favour of daratumumab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone was shown for the outcome constipation. However, the difference is no more than marginal for this outcome in the category of non-serious/non-severe symptoms/late complications. There was no hint of an added benefit of daratumumab + bortezomib + lenalidomide + dexamethasone

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

Symptoms (recorded using the EORTC QLQ-Multiple Myeloma 20 [MY20])

Disease symptoms and side effects

There was no statistically significant difference between the treatment arms for either of the outcomes disease symptoms and side effects. There was no hint of an added benefit of daratumumab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone for any of the outcomes; an added benefit is therefore not proven in each case.

Health status (recorded using the EQ-5D visual analogue scale [VAS])

No statistically significant difference between the treatment arms was shown for the outcome health status, recorded using the EQ-5D VAS. There was no hint of an added benefit of daratumumab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

No statistically significant difference between the treatment arms was shown for any of the outcomes global health status, physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning. There was no hint of an added benefit of daratumumab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone for any of the outcomes; an added benefit is therefore not proven in each case.

EORTC QLQ-MY20

No statistically significant difference between the treatment arms was shown for the outcomes of future perspective and body image. There was no hint of an added benefit of daratumumab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone for any of the outcomes; an added benefit is therefore not proven in each case.

Side effects

Serious adverse events (SAEs), severe AEs, and discontinuation due to AEs

There was no statistically significant difference between treatment arms for either of the outcomes of SAEs, severe AEs or discontinuation due to AEs. There was no hint of greater or lesser harm of daratumumab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone for any of the outcomes; greater or lesser harm is therefore not proven in each case.

Peripheral neuropathy (severe AEs)

There was no statistically significant difference between the treatment arms for the outcome peripheral neuropathy (severe AEs). There was no hint of greater or lesser harm of daratumumab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone; greater or lesser harm is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit³

On the basis of the results presented, the probability and extent of the added benefit of the drug daratumumab + bortezomib + lenalidomide + dexamethasone in comparison with the ACT is assessed as follows:

Neither positive nor negative effects were found for daratumumab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone.

In summary, there is no hint of an added benefit of daratumumab + bortezomib + lenalidomide + dexamethasone versus bortezomib + lenalidomide + dexamethasone for adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant; an added benefit is therefore not proven.

Table 3 shows a summary of the probability and extent of the added benefit of daratumumab in combination with bortezomib, lenalidomide and dexamethasone.

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

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

Therapeutic indication	ACT ^a	Probability and extent of added benefit
Adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant	▪ daratumumab in combination with lenalidomide and dexamethasone or ▪ daratumumab in combination with bortezomib, melphalan and prednisone or ▪ bortezomib in combination with melphalan and prednisone or ▪ bortezomib in combination with lenalidomide and dexamethasone or ▪ thalidomide in combination with melphalan and prednisone or ▪ bortezomib in combination with cyclophosphamide and dexamethasone (only for patients with peripheral polyneuropathy or an increased risk of developing peripheral polyneuropathy^b)	Added benefit not proven
a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company according to the inclusion criteria in Module 4 Section 4.2.2 is printed in bold. b. See Appendix VI to Section K of the Pharmaceutical Directive. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

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

I 2 Research question

The aim of this report is to assess the added benefit of daratumumab in combination with bortezomib, lenalidomide and dexamethasone (hereinafter 'daratumumab + bortezomib + lenalidomide + dexamethasone') in comparison with the appropriate comparator therapy (ACT) in adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (ASCT).

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of daratumumab + bortezomib + lenalidomide + dexamethasone

Therapeutic indication	ACT ^a
Adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant	▪ daratumumab in combination with lenalidomide and dexamethasone - or ▪ daratumumab in combination with bortezomib, melphalan and prednisone - or ▪ bortezomib in combination with melphalan and prednisone - or ▪ bortezomib in combination with lenalidomide and dexamethasone - or ▪ thalidomide in combination with melphalan and prednisone - or ▪ bortezomib in combination with cyclophosphamide and dexamethasone (only for patients with peripheral polyneuropathy or an increased risk of developing peripheral polyneuropathy^b)
a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company according to the inclusion criteria in Module 4 Section 4.2.2 is printed in bold. b. See Appendix VI to Section K of the Pharmaceutical Directive. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA's ACT and named all treatment options in Module 3 A and Module 4 A, but did not consider the option 'daratumumab in combination with bortezomib, melphalan and prednisone' in the inclusion criteria. The company did not justify its approach in the dossier, but presented data for the comparison with bortezomib in combination with lenalidomide and dexamethasone (hereinafter 'bortezomib + lenalidomide +

dexamethasone'). The company's approach had no consequences for this benefit assessment, as no additional relevant study was identified in the review of the completeness of the study pool (see Section I 3).

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used to derive the added benefit. This concurred with the company's inclusion criteria.

I 3 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study list on daratumumab (status: 1 July 2025)
- Bibliographical literature search on daratumumab (last search on 1 July 2025)
- Search of trial registries / trial results databases for studies on daratumumab (last search on 8 July 2025)
- Search on the G-BA website for daratumumab (last search on 9 July 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on daratumumab (last search on 4 September 2025); for search strategies, see I Appendix A of the full dossier assessment

The search did not identify any additional relevant studies.

I 3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: daratumumab + bortezomib + lenalidomide + dexamethasone^a vs. bortezomib + lenalidomide + dexamethasone^b

Study	Study category			Available sources		
	Study for the marketing authorization of the drug to be assessed (yes/no)	Sponsored study ^c (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries ^d (yes/no [citation])	Publication (yes/no [citation])
54767414MMY3019 (CEPHEUS ^e)	Yes	Yes	No	Yes [3,4]	Yes [5-7]	Yes [8,9]
a. Followed by treatment with daratumumab + lenalidomide + dexamethasone in Cycle 9 and beyond. b. Followed by treatment with lenalidomide + dexamethasone in Cycle 9 and beyond. c. Study sponsored by the company. d. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries. e. In the following tables, the study is referred to by this acronym. CSR: clinical study report; RCT: randomized controlled trial						

The study pool for this benefit assessment consists of the CEPHEUS study. However, there were uncertainties regarding the unsuitability of ASCT for the patients included. These

uncertainties and their effect on this benefit assessment are described in Sections I 3.2 and I 4.2.

I 3.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: daratumumab + bortezomib + lenalidomide + dexamethasone^a vs. bortezomib + lenalidomide + dexamethasone^b (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes ^c
CEPHEUS	RCT, open-label, parallel	Adults (≥ 18 years) with newly diagnosed multiple myeloma - who are not candidates for high-dose chemotherapy with ASCT (age ≥ 65 years, or age < 65 years with presence of important comorbid conditions) - who are candidates for high-dose therapy with ASCT, but who have refused this treatment (< 65 years) - ECOG PS ≤ 2	daratumumab + bortezomib + lenalidomide + dexamethasone^a (N = 197) bortezomib + lenalidomide + dexamethasone^b (N = 198) Relevant subpopulation thereof^d: daratumumab + bortezomib + lenalidomide + dexamethasone^a (n = 144) bortezomib + lenalidomide + dexamethasone^b (n = 145)	Screening: up to 28 days Treatment: until disease progression or unacceptable toxicity (bortezomib: 24 weeks max.) Observation^e: outcome-specific, at most until end of study^f	98 centres in: Brazil, Canada, Czech Republic, France, Germany, Israel, Japan, Netherlands, Poland, Spain, Turkey, United Kingdom, United States 11/2018–ongoing Data cut-offs: 08 April 2021^g 08 September 2022^h 7 May 2024ⁱ	Primary: MRD negativity rate Secondary: overall survival, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: daratumumab + bortezomib + lenalidomide + dexamethasone^a vs. bortezomib + lenalidomide + dexamethasone^b (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes ^c
a. Followed by treatment with daratumumab + lenalidomide + dexamethasone in Cycle 9 and beyond. b. Followed by treatment with lenalidomide + dexamethasone in Cycle 9 and beyond. c. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment. d. Patients who are not candidates for high-dose chemotherapy with ASCT, defined as all patients ≥ 70 years, as well as patients < 70 years who are ineligible for ASCT according to the investigator's assessment. Patients < 70 years who had refused ASCT were not included in the relevant subpopulation. e. Outcome-specific information is described in Table 8. f. According to Amendment 6 of the study protocol (14 March 2024), data will be recorded up to 7 years after randomization of the last patient. The study will end on 31 October 2028, or earlier, once all patients have either completed treatment with daratumumab or are no longer receiving daratumumab as part of their participation in the study. According to the information provided by the company in Module 4 A of the dossier, the final data cut-off is expected on 1 September 2026. g. Prespecified primary analysis of the MRD negativity rate planned approx. 18 months after the last patient in the total population received the first dose of the study medication h. Prespecified interim analysis on PFS after 113 PFS events in the total population (planned for after approx. 98 PFS events, when 60% of PFS events had been observed). i. Prespecified final analysis on PFS after 162 PFS events in the total population (planned after approx. 162 PFS events). AE: adverse event; ASCT: autologous stem cell transplantation; ECOG PS: Eastern Cooperative Oncology Group Performance Status; MRD: minimal residual disease; n: relevant subpopulation; N: number of randomized patients; PFS: progression-free survival; RCT: randomized controlled trial						

Table 7: Characteristics of the intervention – RCT, direct comparison: daratumumab + bortezomib + lenalidomide + dexamethasone^a vs. bortezomib + lenalidomide + dexamethasone^b (multipage table)

Study	Intervention	Comparison
CEPHEUS	Daratumumab 1800 mg, SC ▪ Cycle 1–2 (length: 21 days): weekly (Days 1, 8 and 15) ▪ Cycles 3–8 (length: 21 days): every 3 weeks (Day 1) ▪ Cycle 9 and beyond (length: 28 days): every 4 weeks^c + bortezomib 1.3 mg/m² BSA, SC ▪ Cycles 1–8 (length: 21 days): Days 1, 4, 8 and 11 + lenalidomide 25 mg^d, orally ▪ Cycles 1–8 (length: 21 days): Days 1–14 ▪ Cycle 9 and beyond (length: 28 days): Days 1–21^c + dexamethasone^{e, f} (or equivalent), orally ▪ 20 mg in Cycles 1–8 (length: 21 days): Days 1, 2, 4, 5, 8, 9, 11 and 12 ▪ 40 mg in Cycle 9 and beyond (length: 28 days): Days 1, 8, 15 and 22^c	bortezomib 1.3 mg/m² BSA, SC ▪ Cycles 1–8 (length: 21 days): Days 1, 4, 8 and 11 + lenalidomide 25 mg^d, orally ▪ Cycles 1–8 (length: 21 days): Days 1–14 ▪ Cycle 9 and beyond (length: 28 days): Days 1–21^c + dexamethasone^e (or equivalent), orally ▪ 20 mg in Cycles 1–8 (length: 21 days): Days 1, 2, 4, 5, 8, 9, 11 and 12 ▪ 40 mg in Cycle 9 and beyond (length: 28 days): Days 1, 8, 15 and 22^c
	Treatment modifications: ▪ daratumumab: dose modifications not allowed^g ▪ bortezomib, lenalidomide and dexamethasone: dose reductions and discontinuation allowed ▪ Treatment with the remaining components could be continued after discontinuation of one component.	

Table 7: Characteristics of the intervention – RCT, direct comparison: daratumumab + bortezomib + lenalidomide + dexamethasone^a vs. bortezomib + lenalidomide + dexamethasone^b (multipage table)

Study	Intervention	Comparison
	Disallowed prior treatment ▪ Prior therapy for multiple myeloma other than a short course of corticosteroids ▪ Focal radiation therapy (with the exception of palliative radiotherapy for symptomatic pain management, unless used for extramedullary plasmacytoma) within 14 days of randomization, and plasmapheresis within 28 days of randomization Concomitant treatment <u>Required</u> ▪ Premedication before daratumumab injection: dexamethasone 20 mg (Cycles 1–8) and 40 mg (Cycle 9 and beyond) IV or orally^{e, f}; diphenhydramine 25–50 mg IV or orally (or equivalent); paracetamol 650–1000 mg IV or orally; depending on clinical need: in Cycle 1, Day 1: montelukast 10 mg orally (or equivalent) <u>Recommended</u> ▪ Prophylaxis of venous thromboembolism, antibacterial and antiviral prophylaxis ▪ Bisphosphonates or alternatively denosumab ▪ Therapy for tumour lysis syndrome <u>Allowed</u> ▪ After Cycle 4: stem cell collection after mobilization with G-CSF, plerixafor, cyclophosphamide or their combinations ▪ Colony-stimulating factors, erythropoietin, as well as transfusion of platelets and red cells ▪ Emergency treatment with corticosteroids (equivalent of dexamethasone 40 mg/day for a maximum of 4 days) before treatment <u>Disallowed</u> ▪ Agents that target CD38 ▪ Other treatments for multiple myeloma ▪ Systemic corticosteroids (> 10 mg dexamethasone/day or equivalent, or a maximum dose of 140 mg dexamethasone or equivalent in 14 days) other than those given for injection-related reactions	
	a. Followed by treatment with daratumumab + lenalidomide + dexamethasone in Cycle 9 and beyond. b. Followed by treatment with lenalidomide + dexamethasone in Cycle 9 and beyond. c. Until disease progression or unacceptable toxicity d. For patients with creatinine clearance ≥ 60 mL/min e. For patients > 75 years of age or with BMI < 18.5, administration may be as follows: as study medication 20 mg on Days 1, 4, 8, 11 in Cycles 1–8, 20 mg weekly in Cycle 9 and beyond; as premedication prior to daratumumab injection 20 mg. f. In the intervention arm, premedication with dexamethasone IV or orally on the days of daratumumab injection replaced the dexamethasone dose. g. In the event of injection-related reactions (depending on severity), the injection is paused until the patient's condition is stable or until treatment discontinuation. BMI: body mass index; BSA: body surface area; BW: body weight; CD: cluster of differentiation; G-CSF: granulocyte colony-stimulating factor; IV: intravenous; RCT: randomized controlled trial; SC: subcutaneous	

CEPHEUS

The CEPHEUS study is an ongoing, open-label RCT comparing daratumumab + bortezomib + lenalidomide + dexamethasone versus bortezomib + lenalidomide + dexamethasone.

It included patients ≥ 18 years of age with newly diagnosed multiple myeloma as per the International Myeloma Working Group (IMWG) criteria who are not candidates for high-dose chemotherapy with subsequent ASCT or who are candidates for high-dose therapy with subsequent ASCT but who refused this treatment. According to the inclusion criteria, patients were not candidates for high-dose chemotherapy with subsequent ASCT due to age ≥ 65 years, or age < 65 years with presence of relevant comorbid conditions (see also the next section on uncertainties regarding the CEPHEUS study and Section I 4.2). An inclusion due to refusal to have high-dose therapy with subsequent ASCT was therefore only possible for patients < 65 years without relevant comorbidities. In addition, the patients' general health at enrolment had to correspond to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 2.

Patients were randomized in a 1:1 ratio, stratified by International Staging System (ISS) stage (I versus II versus III) and age/ASCT eligibility (≥ 70 years versus < 70 years and ineligible for ASCT versus < 70 years and refusal to have ASCT). A total of 395 patients were randomized to the treatment arms: 197 to the intervention arm and 198 to the comparator arm.

The CEPHEUS study was divided into 2 treatment phases. In Cycles 1 to 8 (cycle length of 21 days), patients in the intervention arm were treated with daratumumab + bortezomib + lenalidomide + dexamethasone and in the comparator arm with bortezomib + lenalidomide + dexamethasone. Subsequently, in Cycle 9 and beyond (cycle length of 28 days), bortezomib was discontinued as part of the study medication in both treatment arms, and patients continued treatment with daratumumab + lenalidomide + dexamethasone or lenalidomide + dexamethasone.

Treatment in the intervention and comparator arm was carried out in compliance with the summaries of product characteristics (SmPCs) [10-13]. In the intervention arm, patients received a premedication before treatment with daratumumab to prevent infusion-related reactions. As part of the premedication, the patients were treated with dexamethasone, diphenhydramine, paracetamol and – depending on clinical necessity – montelukast.

Treatment with the study medication was conducted until disease progression as per IMWG criteria or unacceptable toxicity. If any component of the treatment regimen was discontinued, continued treatment with the remaining components was allowed. Subsequent antineoplastic therapy could only be started after confirmed disease progression. Treatment switching from the comparator arm to the intervention arm was not planned in the CEPHEUS study.

The primary outcome in the CEPHEUS study was the minimal residual disease (MRD) negativity rate (based on a threshold of 10^{-5} malignant plasma cells in the bone marrow). Patient-relevant secondary outcomes included outcomes in the categories of mortality, morbidity, health-related quality of life and side effects.

Data cuts

CEPHEUS is an ongoing study. A total of 3 data cuts are available for CEPHEUS:

- 1st data cut-off of 8 April 2021: prespecified primary analysis of the MRD negativity rate approx. 18 months after the last patient in the total population received the first dose of the study medication
- 2nd data cut-off of 8 September 2022: prespecified interim analysis of progression-free survival (PFS) triggered by the accumulation of 113 PFS events in the total population
- 3rd data cut-off of 7 May 2024: prespecified final analysis of PFS triggered by the accumulation of 162 PFS events in the total population

The 3rd data cut of 7 May 2024 was used for the final analysis of PFS.

According to Amendment 6 of the study protocol (14 March 2024), data will be recorded up to 7 years after randomization of the last patient. The company stated in Module 4 A of the dossier that the final data cut-off is expected on 1 September 2026.

Uncertainties regarding the CEPHEUS study – ASCT ineligibility of the study population questionable

Approach of the company

The therapeutic indication of daratumumab + bortezomib + lenalidomide + dexamethasone to be assessed comprises adult patients with newly diagnosed multiple myeloma who are ineligible for ASCT. According to the inclusion criteria of the CEPHEUS study, high-dose therapy with ASCT was not considered an option for patients who were at least 65 years of age, or who were younger than 65 years and had relevant comorbidities. In addition, patients younger than 65 years who were candidates for high-dose therapy with ASCT, but refused such treatment, were also included. According to the European Medicines Agency (EMA) [14], patients who refuse ASCT, but who are eligible in principle, are not covered by this therapeutic indication. Furthermore, according to current guideline recommendations [15,16], the age criterion alone is not suitable for determining ineligibility for ASCT. Biological age in good general health is currently considered more important than chronological age when assessing eligibility for ASCT. It is difficult to define a maximum age for ASCT. Instead, individual patient factors should be considered when making treatment decisions, taking into account the patient's general condition, existing comorbidities, functional status and social integration [16]. For the operationalization of ASCT ineligibility, it is therefore not appropriate to

determine patient ineligibility for ASCT solely on the basis of age, as was done in the inclusion criteria of the CEPHEUS study for patients ≥ 65 years. However, in accordance with the electronic case report form (eCRF), the investigators also carried out an individual assessment of each patient's eligibility or ineligibility for ASCT for all patients under the age of 70 in the CEPHEUS study. It was unclear exactly which criteria the investigators used for the individual patient assessment of ASCT eligibility or ineligibility. However, among other tools, the Charlson Comorbidity Index (CCI) was used in the study to record the presence of relevant comorbidities (e.g. diabetes mellitus, dementia, myocardial infarction). It was therefore assumed that the results of this recording were taken into account in the assessment of ASCT eligibility or ineligibility by the investigator.

In Module 4 A, the company addressed the operationalization of ASCT ineligibility in the CEPHEUS study to represent the population under assessment, and presented post-hoc analyses for the 'ASCT ineligible' subpopulation as an approximation of a population ineligible for ASCT. This subpopulation included the following patients:

- Age < 70 years who are ineligible for ASCT according to the investigator's assessment
- Age ≥ 70 years

In the CEPHEUS study, 73% (289 of 395) of the patients included in the total population fulfilled these criteria. However, the information on the characteristic of age in the subpopulation showed that the subpopulation mainly included patients ≥ 70 years of age (76%) (see Table 9).

In Module 4 A, the company also presented post hoc analyses of the subpopulation 'ASCT ineligible according to EMA criteria' in the form of subgroup analyses based on the subpopulation described above. To form this subpopulation, the company chose the same operationalization as the one presented in dossier assessments A18-66 [17] and A23-127 [18] on daratumumab, as well as in A25-20 [19] on isatuximab. The operationalization for ASCT ineligibility according to EMA criteria comprised the following patients:

- Age < 65 years with important comorbidities
- Age 65 to 69 years with ECOG PS = 2
- Age ≥ 70 years

These criteria were met by 79% (227 of 289) of the patients in the 'ASCT ineligible' subpopulation. The subpopulation 'ASCT ineligible according to EMA criteria' differed from the subpopulation 'ASCT ineligible' in that patients aged 65 to 69 with an ECOG PS of 0 or 1 were generally excluded from the subpopulation 'ASCT ineligible according to EMA criteria'. This meant that 62 patients from the 'ASCT ineligible' subpopulation were excluded.

In Module 4 A, the company used the 'ASCT ineligible' subpopulation to derive the added benefit.

Assessment of the company's approach and consequences for the benefit assessment

The creation of the 'ASCT ineligible' subpopulation by excluding patients who are eligible for ASCT (27% of the total population, comprising patients who refused ASCT), and, based on this, the creation of the 'ASCT ineligible according to EMA criteria' subpopulation by the company, is understandable. This achieved an approximation to the research question population relevant to the benefit assessment. However, there were uncertainties in both subpopulations, which are described below.

In the CEPHEUS study, the investigators carried out an individual assessment of each patient's eligibility or ineligibility for ASCT for all patients under the age of 70. Such an individual assessment was therefore only carried out for 24% of the patients in the 'ASCT ineligible' subpopulation. The individual assessment was not carried out for patients aged ≥ 70 (76% of the 'ASCT ineligible' subpopulation) and it was not possible to determine the corresponding information post hoc. Hence there was the uncertainty that the exact proportion of patients in this subpopulation for whom ASCT would actually not have been suitable on an individual basis was unclear.

In addition to the 'ASCT ineligible' subpopulation, the company provided analyses of the 'ASCT ineligible according to EMA criteria' subpopulation in the form of subgroup analyses. In Module 4 A, the company described that the comparison of the patient characteristics and the analyses between the populations did not reveal any differences relevant for the benefit assessment. This assessment was appropriate. One reason for this was that the results between the 'ASCT ineligible' subpopulation and the 'ASCT ineligible according to EMA criteria' subpopulation were generally very similar for the decision-relevant outcomes. Another reason was that there were no consistent and relevant effect modifications by the characteristic 'ASCT ineligibility' / 'ASCT eligibility' (subgroups presented by the company: 'ASCT ineligible according to EMA criteria' versus 'ASCT eligible according to EMA criteria' [patients aged 65 to 69 years with an ECOG PS of 0 or 1]).

Since the difference between the 'ASCT ineligible' subpopulation and the 'ASCT ineligible according to EMA criteria' subpopulation was based solely on patients who received an individual assessment regarding ASCT ineligibility (65 to 69-year-olds with ECOG 0 to 1 in the 'ASCT ineligible' subpopulation), the 'ASCT ineligible' subpopulation was overall a better approximation to the target population. Since, in addition, comparable results were observed between the subpopulations, the results for the 'ASCT ineligible' subpopulation were used for this benefit assessment, in an analogous manner to the approach used by the company.

However, this subpopulation was still subject to uncertainty (see previous explanations). This uncertainty was taken into account in the certainty of conclusions (see Section I 4.2).

Planned duration of follow-up

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

Table 8: Planned duration of follow-up – RCT, direct comparison: daratumumab + bortezomib + lenalidomide + dexamethasone^a vs. bortezomib + lenalidomide + dexamethasone^b

Study	Planned follow-up
Outcome category	
Outcome	
CEPHEUS	
Mortality	
Overall survival	Until death, lost to follow-up, withdrawal of consent or end of study (whichever occurred first)
Morbidity	
Symptoms (EORTC QLQ-C30, EORTC QLQ-MY20)	Up to 30 days after the last dose of study medication or up to 4 weeks after the start of subsequent therapy (if subsequent therapy was administered)
Health status (EQ-5D VAS)	Until death, lost to follow-up, withdrawal of consent or end of study (whichever occurred first)
Health-related quality of life	
EORTC QLQ-C30, EORTC QLQ-MY20	Up to 30 days after the last dose of study medication or up to 4 weeks after the start of subsequent therapy (if subsequent therapy was administered)
Side effects	
All outcomes in the side effects category	Up to 30 days after the last dose of the study medication ^c
a. Followed by treatment with daratumumab + lenalidomide + dexamethasone in Cycle 9 and beyond. b. Followed by treatment with lenalidomide + dexamethasone in Cycle 9 and beyond. c. Treatment-related SAEs were recorded beyond this period. EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma 20; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale	

Observation for the outcomes overall survival and health status (EQ-5D visual analogue scale [VAS]) took place until death, lost to follow-up, withdrawal of consent, or end of study (whichever occurred first). The observation periods for the outcomes in the categories of morbidity and health-related quality of life – with the exception of the health status outcome (EQ-5D VAS) – and the outcomes in the side effects category were systematically shortened, as they were only recorded for the period of treatment with the study medication (plus 30 days) or until the start of subsequent therapy (plus 4 weeks). However, to draw a reliable

conclusion on the total study period or the time to patient death, it would also be necessary to record these outcomes for the total period, as was done for survival and health status.

Characteristics of the relevant subpopulation

Table 9 shows the patient characteristics of the relevant subpopulation in the included study.

Table 9: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: daratumumab + bortezomib + lenalidomide + dexamethasone^a vs. bortezomib + lenalidomide + dexamethasone^b, relevant subpopulation (multipage table)

Study Characteristic Category	daratumumab + bortezomib + lenalidomide + dexamethasone ^a N ^c = 144	bortezomib + lenalidomide + dexamethasone ^b N ^c = 145
CEPHEUS		
Age [years], n (%)		
< 65	2 (1)	2 (1)
65 – < 70	33 (23)	33 (23)
≥ 70	109 (76)	110 (76)
Sex [F/M], %	55/45	43/57
Family origin, n (%)		
White	122 (85)	112 (77)
Black or African American	4 (3)	8 (6)
Asian	7 (5)	12 (8)
Other ^d	1 (<1)	2 (1) ^e
Not reported	10 (7)	11 (8)
ECOG PS at baseline, n (%)		
0	52 (36)	57 (39)
1	75 (52)	78 (54)
2	17 (12)	10 (7)
ISS stage ^f , n (%)		
I	50 (35)	48 (33)
II	54 (38)	57 (39)
III	40 (28)	40 (28)
Disease duration: time since initial diagnosis [months], mean (SD)	1.5 (1.0)	1.5 (1.1)
Number of lytic bone lesions, n (%)		
None	27 (19)	41 (28)
1 – 10	67 (47) ^e	63 (43) ^e
> 10	50 (35)	41 (28)
Presence of extramedullary plasmacytomas, n (%)	9 (6)	12 (8)

Table 9: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: daratumumab + bortezomib + lenalidomide + dexamethasone^a vs. bortezomib + lenalidomide + dexamethasone^b, relevant subpopulation (multipage table)

Study Characteristic Category	daratumumab + bortezomib + lenalidomide + dexamethasone ^a N ^c = 144	bortezomib + lenalidomide + dexamethasone ^b N ^c = 145
Percentage of plasma cells in the bone marrow (biopsy/aspirate)		
< 10	4 (3)	3 (2)
10 – 30	66 (46)	77 (53)
> 30 – 60	43 (30)	35 (24)
> 60	31 (22)	30 (21)
Cytogenetic risk ^g , n (%)		
Standard risk	105 (73)	111 (77)
High risk	20 (14)	18 (12)
Unknown	19 (13)	16 (11)
Treatment discontinuation, n (%) ^h	ND	ND
Study discontinuation, n (%) ⁱ	ND	ND
a. Followed by treatment with daratumumab + lenalidomide + dexamethasone in Cycle 9 and beyond. b. Followed by treatment with lenalidomide + dexamethasone in Cycle 9 and beyond. c. Number of randomized patients in the relevant subpopulation. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant. d. Includes Native Hawaiians or Other Pacific Islanders and other. e. Institute's calculation. f. ISS staging is derived based on the combination of serum β2-microglobulin and albumin. g. Determined by FISH; standard risk defined as negative for del(17p), t(14;16) or t(4;14); high risk defined as positive for del(17p), t(14;16) or t(4;14). h. Data only available for the total population [N = 197 vs. N = 198]. In the total population, treatment discontinuations occurred in 95 (48%) patients in the intervention arm and in 128 (65%) patients in the comparator arm. Common reasons for treatment discontinuation in the intervention vs. the comparator arm were disease progression (14% vs. 26%), AE (8% vs. 16%) and patient decision (8 % vs. 4 %). In addition, 0 vs. 3 (2%) of the randomized patients never started treatment. The data additionally include patients who died during the course of the study (intervention arm: 17% vs. comparator arm: 12%). i. Data only available for the total population [N = 197 vs. N = 198]. In the total population, study discontinuations occurred in 62 (31%) patients in the intervention arm and in 69 (35%) patients in the comparator arm. Common reasons for study discontinuation in the intervention vs. the comparator arm were patient decision (6 % vs. 7 %) and lost to follow-up (< 1 % vs. 1 %). The data additionally include patients who died during the course of the study (intervention arm: 25% vs. comparator arm: 27%). ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; FISH: fluorescence in situ hybridization; ISS: International Staging System; M: male; n: number of patients in the category; N: number of randomized patients in the relevant subpopulation; RCT: randomized controlled trial; SD: standard deviation		

Overall, the patient characteristics for the relevant subpopulation were largely comparable between the 2 treatment arms. In both treatment arms, the majority of patients were ≥ 70 years old (76%) and of white family origin (85% in the intervention arm, 77% in the

comparator arm). The majority (approx. 90%) of patients had an ECOG PS of 0 or 1. The patients included had International Staging System (ISS) stage I (34%), II (38%) or III (28%) disease. At baseline, around half of the patients had a plasma proportion of 10 % to 30 % in the bone marrow. Furthermore, 81% of patients in the intervention arm and 72% of those in the comparator arm had bone marrow lesions at baseline. The cytogenetic risk profile was comparable between the treatment arms, with the majority of patients (75 %) having a standard risk.

Information on treatment and study discontinuations were only available for the total population of the CEPHEUS study. At the given data cut-off, there was a clear difference in treatment discontinuations between the treatment arms (48% versus 65%). This difference was due in particular to the higher proportion of disease progression (14% versus 26%) and adverse events (AEs) (8% versus 16%) as a reason for treatment discontinuation in the comparator arm.

Course of the study

Table 10 shows the median treatment duration of the patients and the median observation period for individual outcomes. In the dossier, the company did not provide any information on the mean treatment duration or the mean observation period for individual outcomes for the relevant subpopulation.

Table 10: Information on the course of the study – RCT, direct comparison: daratumumab+ bortezomib + lenalidomide + dexamethasone^a vs. bortezomib + lenalidomide + dexamethasone^b, relevant subpopulation

Study Duration of the study phase Outcome category/outcome	daratumumab + bortezomib + lenalidomide + dexamethasone ^a N = 144	bortezomib + lenalidomide + dexamethasone ^b N = 145
CEPHEUS		
Treatment duration [months]		
Median [min; max]	55.3 [ND]	34.0 [ND]
Mean (SD)	ND	ND
Observation period [months]		
Overall survival ^c		
Median [min; max]	58.7 [ND]	58.9 [ND]
Mean (SD)	ND	ND
Morbidity, health-related quality of life		
EORTC QLQ-C30		
Median [min; max]	53.2 [ND]	38.2 [ND]
Mean (SD)	ND	ND
EORTC QLQ-MY20		
Median [min; max]	52.6 [ND]	38.2 [ND]
Mean (SD)	ND	ND
EQ-5D VAS		
Median [min; max]	54.2 [ND]	52.2 [ND]
Mean (SD)	ND	ND
Side effects		
Median [min; max]	56.3 [ND]	35.0 [ND]
Mean (SD)	ND	ND
a. Followed by treatment with daratumumab + lenalidomide + dexamethasone in Cycle 9 and beyond. b. Followed by treatment with lenalidomide + dexamethasone in Cycle 9 and beyond. c. Calculated using the inverse Kaplan-Meier method. 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; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma 20; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale		

For the relevant subpopulation, the median treatment duration in the CEPHEUS study was notably longer in the intervention arm (approx. 55 months) than in the comparator arm (34 months).

The median observation period for the outcome of overall survival was comparable between the treatment arms (about 59 months). The observation period between the treatment arms was also comparable for the outcome health status (recorded using the EQ-5D VAS) (approx. 54 months versus approx. 52 months). Since the observation periods for the outcomes in the categories of morbidity (except EQ-5D VAS), health-related quality of life and side effects were linked to the treatment duration (see Table 8), the median observation periods for these outcomes were notably longer in the intervention arm than in the comparator (approx. 53 to 56 months versus 35 to 38 months).

Subsequent therapies

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

Table 11: Information on subsequent antineoplastic therapies (≥ 2 patients in both treatment arms combined) – RCT, direct comparison: daratumumab + bortezomib + lenalidomide + dexamethasone^a vs. bortezomib + lenalidomide + dexamethasone^b, relevant subpopulation (multipage table)

Study Drug	Patients with subsequent therapy, n (%)	
	daratumumab + bortezomib + lenalidomide + dexamethasone ^a N = 144	bortezomib + lenalidomide + dexamethasone ^b N = 145
CEPHEUS		
Proportion of randomized patients with at least 1 subsequent therapy	19 (13.2 ^c)	53 (36.6 ^c)
Proportion of randomized patients with at least 2 subsequent therapies	6 (4.2 ^c)	17 (11.7 ^c)
1st subsequent therapy ^d		
carfilzomib-dexamethasone	3 (15.8 ^c)	1 (1.9 ^c)
carfilzomib-dexamethasone- pomalidomide	2 (10.5 ^c)	0 (0)
bortezomib-cyclophosphamide- dexamethasone	1 (5.3 ^c)	1 (1.9 ^c)
bortezomib-dexamethasone	1 (5.3 ^c)	1 (1.9 ^c)
bortezomib-dexamethasone- pomalidomide	1 (5.3 ^c)	1 (1.9 ^c)
bortezomib-melphalan-prednisone	1 (5.3 ^c)	1 (1.9 ^c)
daratumumab-dexamethasone- lenalidomide	1 (5.3 ^c)	3 (5.7 ^c)
dexamethasone-ixazomib-lenalidomide	1 (5.3 ^c)	1 (1.9 ^c)
lenalidomide	1 (5.3 ^c)	1 (1.9 ^c)
monoclonal antibodies	1 (5.3 ^c)	1 (1.9 ^c)
bortezomib-daratumumab- dexamethasone	0 (0)	8 (15.1 ^c)
carfilzomib-daratumumab- dexamethasone	0 (0)	2 (3.8 ^c)
daratumumab-dexamethasone- pomalidomide	0 (0)	3 (5.7 ^c)
dexamethasone-isatuximab- pomalidomide	0 (0)	3 (5.7 ^c)
dexamethasone-lenalidomide	0 (0)	2 (3.8 ^c)
dexamethasone-pomalidomide	0 (0)	3 (5.7 ^c)
investigational drug	0 (0)	2 (3.8 ^c)

Table 11: Information on subsequent antineoplastic therapies (≥ 2 patients in both treatment arms combined) – RCT, direct comparison: daratumumab + bortezomib + lenalidomide + dexamethasone^a vs. bortezomib + lenalidomide + dexamethasone^b, relevant subpopulation (multipage table)

Study Drug	Patients with subsequent therapy, n (%)	
	daratumumab + bortezomib + lenalidomide + dexamethasone ^a N = 144	bortezomib + lenalidomide + dexamethasone ^b N = 145
2nd subsequent therapy		
carfilzomib	1 (16.7 ^c)	1 (5.9 ^c)
cyclophosphamide-dexamethasone-pomalidomide	1 (16.7 ^c)	1 (5.9 ^c)
daratumumab	0 (0)	2 (11.8 ^c)
daratumumab-dexamethasone-pomalidomide	0 (0)	2 (11.8 ^c)
a. Followed by treatment with daratumumab + lenalidomide + dexamethasone in Cycle 9 and beyond. b. Followed by treatment with lenalidomide + dexamethasone in Cycle 9 and beyond. c. Institute's calculation. d. The following percentages relate to patients with at least 1 subsequent therapy. e. The following percentages relate to patients with at least 2 subsequent therapies. n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial		

Subsequent antineoplastic therapy could only be started after confirmed disease progression. There were no restrictions regarding subsequent therapy and the decision was made by the investigator. Treatment switching from the comparator arm to the intervention arm was not planned in the CEPHEUS study.

Based on the 7 May 2024 data cut, in the relevant subpopulation, 19 (approx. 13%) of the patients in the intervention arm and 53 (approx. 37%) of the patients in the comparator arm received at least one subsequent therapy. Since only patients with disease progression received subsequent therapy, it could be inferred from the numbers of patients with PFS event ($n = 44$ versus $n = 69$, including death without prior disease progression) that 43% of patients with PFS event in the intervention arm and 77% of patients with PFS event in the comparator arm received subsequent therapy. However, it was not clear from the available data how many patients died without prior disease progression and initiation of subsequent therapy or whether a relevant proportion of patients had not (yet) received subsequent therapy.

Overall, the treatments administered in the intervention and comparator arm (including cluster of differentiation (CD)38 antibodies, immunomodulators and proteasome inhibitors) reflected the diversity of treatment options in the therapeutic indication. However, some treatments were administered that did not comply with the recommendations of the current

German and European guidelines [15,20] (such as subsequent therapy with lenalidomide or carfilzomib as monotherapy).

According to the recommendations of the German Society for Haematology and Medical Oncology (DGHO), treatment recommendations for recurrence or refractoriness are based on the type of treatment previously used (substance class) and the previous course of the disease [15]. Patients with disease progression during the course of the CEPHEUS study were assumed to be refractory to lenalidomide (and potentially also to the other treatment components of the study medication). In such a situation (patients who are refractory to lenalidomide and have not been pretreated with a CD38 antibody), the DGHO recommends treatment with a CD38 antibody (daratumumab or isatuximab) in combination with dexamethasone and an immunomodulator (pomalidomide) or with dexamethasone and a proteasome inhibitor (carfilzomib or bortezomib) [15]. The guidelines of the European Hematology Association (EHA) and the European Myeloma Network (EMN) also specify the treatment options in the second line depending on whether the patients have been pretreated with a CD38 antibody or are refractory to this substance and to what extent there is refractoriness to lenalidomide or bortezomib. A CD38 antibody (daratumumab or isatuximab) in combination with dexamethasone and the proteasome inhibitor carfilzomib is also recommended here [20].

In the comparator arm, only 53% (28 out of 53) of the patients with at least one subsequent therapy received treatment with a CD38 antibody (daratumumab or isatuximab) in the first subsequent therapy. This therapy was hardly used in later lines of treatment. Assuming that the patients with disease progression were refractory to lenalidomide (see above), only 32% (17 of 53) of the patients in the comparator arm received an appropriate first subsequent therapy using a CD38 antibody in accordance with the DGHO treatment recommendations [15]. It was assumed that a relevant proportion of patients would have benefited from subsequent therapy containing CD38 antibodies.

Based on the available data, it was overall assumed that the subsequent therapies administered in CEPHEUS did not adequately reflect the current standard of care. In particular, it was critically noted that the marketing authorization for daratumumab (as monotherapy in May 2016, and as combination therapy in April 2017) for second-line treatment had already been granted before the start of the study, so that daratumumab could have been used as subsequent therapy within the CEPHEUS study. The deficiencies regarding the subsequent therapies used were taken into account for the outcomes overall survival and health status (EQ-5D VAS) in the assessment of the outcome-specific risk of bias (see Section I 4.2).

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 + bortezomib + lenalidomide + dexamethasone^a vs. bortezomib + lenalidomide + dexamethasone^b

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
CEPHEUS	Yes	Yes	No	No	Yes	Yes	Low
a. Followed by treatment with daratumumab + lenalidomide + dexamethasone in Cycle 9 and beyond.							
b. Followed by treatment with lenalidomide + dexamethasone in Cycle 9 and beyond.							
RCT: randomized controlled trial							

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

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

Transferability of the study results to the German health care context

The company described that the CEPHEUS study was conducted at a total of 98 centres worldwide. The participating countries included study centres in Brazil, Canada, the Czech Republic, France, Germany, Israel, Japan, the Netherlands, Poland, Spain, Turkey, the United Kingdom and the United States.

Furthermore, the company stated that the patients included in the analysis population only included patients ≥ 70 years of age, and patients younger than 70 years who the physician assessed as ineligible for ASCT at screening. According to the company, this approach was in line with common clinical practice [21].

The company added that more than half of the study participants (59.7 %) were included in Europe, and that just over 80 % of the study participants included in the CEPHEUS study were of white family origin (intervention arm: 82.2 %, comparator arm: 78.8 %). Moreover, the CEPHEUS study showed no signs of biodynamic or kinetic differences between the individual population groups or countries involved versus Germany to the extent that they would have a significant impact on the study results. Therefore, the company deemed it safe to assume that, taking into account the uncertainty associated with the transferability of clinical data, the results of CEPHEUS were 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.

I 4 Results on added benefit

I 4.1 Outcomes included

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

- Mortality
 - Overall survival
- Morbidity
 - Symptoms, recorded using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and the EORTC QLQ-Multiple Myeloma 20 (MY20)
 - Health status, recorded using the EQ-5D visual analogue scale (VAS)
- Health-related quality of life
 - recorded using EORTC QLQ-C30 and EORTC QLQ-MY20
- Side effects
 - Serious adverse events (SAEs)
 - Severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
 - Discontinuation due to AEs
 - Peripheral neuropathy (High Level Term [HLT], severe AEs)
 - Other specific AEs, if any

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

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

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

Study	Outcomes								
	Overall survival	Symptoms (EORTC QLQ-C30, EORTC QLQ-MY20)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-MY20)	SAEs	Severe AEs ^c	Discontinuation due to AEs	Peripheral neuropathy (HLT, severe AEs ^c)	Other specific AEs
CEPHEUS	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No ^d
a. Followed by treatment with daratumumab + lenalidomide + dexamethasone in Cycle 9 and beyond. b. Followed by treatment with lenalidomide + dexamethasone in Cycle 9 and beyond. c. Severe AEs are operationalized as CTCAE grade ≥ 3. d. No further specific AEs were identified based on the AEs occurring in the relevant study. AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HLT: High Level Term; MedDRA: Medical Dictionary for Regulatory Activities; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma 20; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale									

Notes on outcomes

Outcomes in the categories morbidity and health-related quality of life

For the patient-reported outcomes in the categories of morbidity and health-related quality of life, the statistical analysis plan (SAP) prespecified both analyses of change from baseline using a mixed-effects model with repeated measures (MMRM) and analyses of time to deterioration or improvement. In the SAP, the response threshold for deterioration or improvement was predefined as half the standard deviation of the mean value of both treatment arms at baseline.

Due to the expected progressive course of the disease in the given therapeutic indication, an analysis of the deterioration in symptoms and health-related quality of life was primarily relevant for this benefit assessment. In Module 4 A, the company presented responder analyses for the outcomes on morbidity and health-related quality of life recorded using the EORTC QLQ-C30 and the additional module EORTC QLQ-MY20, in each case for time to first deterioration with a post hoc defined response threshold of ≥ 10 points (respective scale range 0 to 100); and for the outcome health status recorded using the EQ-5D VAS responder analyses for the time to first deterioration with a post hoc defined response threshold of

≥ 15 points (scale range 0 to 100). Since health status (EQ-5D VAS) was also recorded beyond disease progression until the end of the study (or death, lost to follow-up or withdrawal of consent, whichever occurred first), analyses of confirmed or permanent deterioration would have potentially been relevant. This benefit assessment used the responder analyses presented by the company for the time to first deterioration by ≥ 10 points (EORTC QLQ-C30 and EORTC QLQ-MY20) and by ≥ 15 points (EQ-5D VAS).

Outcomes in the category of side effects

Discontinuation due to AEs

For the outcome discontinuation due to AEs, Module 4 A contained both analyses of the time to discontinuation of at least one drug component and analyses of the time to discontinuation of all drug components. Patients in the CEPHEUS study could continue treatment with the remaining drug components after discontinuing one drug component. Given the available data, an analysis on the discontinuation of all drug components alone could not be meaningfully interpreted (up to 4 drug components in the intervention arm and up to 3 drug components in the comparator arm). Regardless of this, analyses on the discontinuation of at least one drug component are preferable, as any AE leading to discontinuation of any treatment component is relevant. Consequently, results for the analysis of the time to discontinuation of at least one drug component were used for the benefit assessment.

Peripheral neuropathy

In the therapeutic indication in question, peripheral neuropathy events are relevant AEs during treatment with bortezomib. In the SAP, the company prespecified peripheral neuropathies as 'AEs of clinical interest' and recorded them using the High Level Term (HLT) on peripheral neuropathy. For this outcome, time-to-event analyses, including severity classification according to CTCAE grade ≥ 3, were available in Module 4 A. The operationalization of severe peripheral neuropathy (CTCAE grade ≥ 3) was patient-relevant and was used for this benefit assessment.

I 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 + bortezomib + lenalidomide + dexamethasone^a vs. bortezomib + lenalidomide + dexamethasone^b

Study	Study level	Outcomes								
		Overall survival	Symptoms (EORTC QLQ-C30, EORTC QLQ-MY20)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-MY20)	SAEs	Severe AEs ^c	Discontinuation due to AEs	Peripheral neuropathy (HLT, severe AEs ^c)	Other specific AEs
CEPHEUS	L	H ^d	H ^{e, f}	H ^{d, f, g}	H ^{e, f}	H ^e	H ^e	H ^f	H ^e	–

a. Followed by treatment with daratumumab + lenalidomide + dexamethasone in Cycle 9 and beyond.
b. Followed by treatment with lenalidomide + dexamethasone in Cycle 9 and beyond.
c. Severe AEs are operationalized as CTCAE grade ≥ 3.
d. Due to uncertainties in the appropriate use of subsequent therapies.
e. Incomplete observations for potentially informative reasons because of differing follow-ups.
f. Lack of blinding in subjective recording of outcomes or subjective decision to discontinue.
g. Large proportion of patients (> 10%) not considered in the analysis.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; H: high; HLT: High Level Term; L: low; MedDRA: Medical Dictionary for Regulatory Activities; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma 20; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

The risk of bias in the results for all outcomes was rated as high. The high risk of bias in the results for the outcome overall survival was due to inappropriate subsequent therapies (see subsequent therapies in Section I 3.2).

For the patient-reported outcomes (symptoms recorded via the EORTC QLQ-C30 and the EORTC QLQ-MY20, health status recorded via the EQ-5D VAS, and health-related quality of life recorded via the EORTC QLQ-C30 and the EORTC QLQ-MY20) and for the outcome discontinuation due to AEs in the side effects category, the risk of bias in the results was rated as high in each case due to a lack of blinding in subjective recording of outcomes or subjective decision to discontinue. In addition, the risk of bias in the results of these patient-reported outcomes (with the exception of the EQ-5D VAS) and the outcomes in the side effects category (SAEs, severe AEs and the specific AE peripheral neuropathy) was assessed as high due to incomplete observations for potentially informative reasons with different follow-ups between the treatment groups.

There were 2 further reasons for the high risk of bias in the results of the health status outcome (EQ-5D VAS). Firstly, there was the high proportion of patients (> 10 %) who were not included in the analysis, as only patients with a baseline value and at least one subsequent value were included in the analysis and this proportion was less than 90 % of the intention-to-treat (ITT) population. In addition, it remained unclear how the inappropriate subsequent therapies affected the observed effects.

Summary assessment of the certainty of conclusions

Irrespective of the aspects described under the risk of bias, the certainty of conclusions of the study results was limited due to the uncertainties described in Section I 3.2 regarding ASCT ineligibility of the relevant subpopulation included. The results of the CEPHEUS study can therefore at most be used to derive hints, for example of an added benefit.

I 4.3 Results

Table 15 summarizes the results of the comparison of daratumumab + bortezomib + lenalidomide + dexamethasone with bortezomib + lenalidomide + dexamethasone in patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplantation. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

The Kaplan-Meier curves for the time-to-event analyses of the outcomes in the included CEPHEUS study are shown in I Appendix B of the full dossier assessment. The results on common AEs, SAEs, severe AEs and discontinuations due to AEs can be found in I Appendix C of the full dossier assessment.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: daratumumab + bortezomib + lenalidomide + dexamethasone^a vs. bortezomib + lenalidomide + dexamethasone^b, relevant subpopulation (multipage table)

Study Outcome category Outcome	daratumumab + bortezomib + lenalidomide + dexamethasone ^a		bortezomib + lenalidomide + dexamethasone ^b		daratumumab + bortezomib + lenalidomide + dexamethasone ^a vs. bortezomib + lenalidomide + dexamethasone ^b
	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 ^c
CEPHEUS					
Mortality					
Overall survival	144	NA 33 (22.9)	145	NA [61.9; NC] 47 (32.4)	0.66 [0.42; 1.03]; 0.070
Morbidity					
Symptoms (EORTC QLQ-C30 – time to first deterioration) ^{d, e}					
Fatigue	138	1.5 [1.0; 1.7] 100 (72.5 ^f)	137	1.5 [1.5; 2.2] 102 (74.5 ^f)	1.09 [0.82; 1.45]; 0.569
Nausea and vomiting	138	6.0 [4.2; 16.9] 83 (60.1 ^f)	137	11.4 [4.5; 42.6] 69 (50.4 ^f)	1.22 [0.88; 1.69]; 0.232
Pain	138	3.7 [2.3; 8.4] 79 (57.2 ^f)	137	3.5 [2.8; 4.0] 88 (64.2 ^f)	0.91 [0.67; 1.24]; 0.549
Dyspnoea	138	3.1 [2.2; 3.7] 101 (73.2 ^f)	137	5.3 [2.9; 11.1] 87 (63.5 ^f)	1.24 [0.93; 1.66]; 0.152
Insomnia	138	2.8 [1.8; 3.9] 100 (72.5 ^f)	137	2.8 [2.2; 4.2] 93 (67.9 ^f)	1.03 [0.77; 1.38]; 0.834
Appetite loss	138	4.3 [3.5; 5.1] 100 (72.5 ^f)	137	3.6 [2.6; 4.5] 96 (70.1 ^f)	0.94 [0.70; 1.24]; 0.644
Constipation	138	3.1 [1.6; 5.6] 92 (66.7 ^f)	137	1.6 [1.4; 2.4] 106 (77.4 ^f)	0.69 [0.51; 0.92]; 0.011
Diarrhoea	138	4.7 [3.5; 6.0] 113 (81.9 ^f)	137	3.7 [2.8; 4.4] 107 (78.1 ^f)	0.88 [0.67; 1.16]; 0.368

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: daratumumab + bortezomib + lenalidomide + dexamethasone^a vs. bortezomib + lenalidomide + dexamethasone^b, relevant subpopulation (multipage table)

Study Outcome category Outcome	daratumumab + bortezomib + lenalidomide + dexamethasone ^a		bortezomib + lenalidomide + dexamethasone ^b		daratumumab + bortezomib + lenalidomide + dexamethasone ^a vs. bortezomib + lenalidomide + dexamethasone ^b HR [95% CI]; p-value ^c
	N	Median time to event in months [95% CI]	N	Median time to event in months [95% CI]	
		Patients with event n (%)		Patients with event n (%)	
Symptoms (EORTC QLQ-MY20 – time to first deterioration ^{d, e})					
Disease symptoms	136	11.6 [4.6; 26.9] 71 (52.2 ^f)	135	13.9 [7.5; 30.9] 74 (54.8 ^f)	1.09 [0.78; 1.52]; 0.619
Side effects	136	2.4 [2.1; 3.5] 96 (70.6 ^f)	135	2.9 [2.1; 4.2] 91 (67.4 ^f)	1.19 [0.88; 1.59]; 0.255
Health status (EQ-5D VAS – time to first deterioration) ^{e, g}	121	4.2 [3.0; 18.7] 71 (58.7 ^f)	125	6.5 [3.5; 43.2] 70 (56.0 ^f)	1.14 [0.81; 1.60]; 0.450
Health-related quality of life					
EORTC QLQ-C30 – time to first deterioration ^{e, h}					
Global health status	138	2.1 [1.6; 3.2] 86 (62.3 ^f)	137	2.8 [2.2; 4.4] 82 (59.9 ^f)	1.19 [0.87; 1.63]; 0.276
Physical functioning	138	3.0 [1.7; 4.3] 89 (64.5 ^f)	137	3.5 [2.8; 4.5] 92 (67.2 ^f)	1.10 [0.82; 1.49]; 0.526
Role functioning	138	2.1 [1.5; 3.1] 89 (64.5 ^f)	137	2.8 [2.1; 3.6] 91 (66.4 ^f)	1.04 [0.77; 1.41]; 0.788
Emotional functioning	138	9.3 [3.3; 23.3] 74 (53.6 ^f)	137	5.3 [3.5; 12.5] 82 (59.9 ^f)	0.89 [0.64; 1.23]; 0.466
Cognitive functioning	138	2.6 [1.8; 3.5] 103 (74.6 ^f)	137	3.5 [2.3; 4.9] 102 (74.5 ^f)	1.18 [0.89; 1.56]; 0.260
Social functioning	138	2.8 [1.5; 3.3] 92 (66.7 ^f)	137	2.6 [1.8; 3.2] 94 (68.6 ^f)	0.98 [0.73; 1.32]; 0.889
EORTC QLQ-MY20 – time to first deterioration ^{e, h}					
Future perspective	136	8.4 [2.8; 54.4] 68 (50.0 ^f)	135	13.7 [4.2; 36.1] 72 (53.3 ^f)	1.03 [0.74; 1.45]; 0.844
Body image	136	8.8 [3.5; 16.6] 78 (57.4 ^f)	135	11.6 [4.2; 50.5] 66 (48.9 ^f)	1.29 [0.93; 1.80]; 0.133

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: daratumumab + bortezomib + lenalidomide + dexamethasone^a vs. bortezomib + lenalidomide + dexamethasone^b, relevant subpopulation (multipage table)

Study Outcome category Outcome	daratumumab + bortezomib + lenalidomide + dexamethasone ^a		bortezomib + lenalidomide + dexamethasone ^b		daratumumab + bortezomib + lenalidomide + dexamethasone ^a vs. bortezomib + lenalidomide + dexamethasone ^b
	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 ^c
Side effects					
AEs (supplementary information)	144	0.1 [0.1; 0.3] 144 (100)	142	0.2 [0.1; 0.3] 142 (100)	–
SAEs	144	12.3 [5.5; 22.1] 104 (72.2)	142	8.3 [4.0; 16.6] 99 (69.7)	0.93 [0.70; 1.23]; 0.600
Severe AEs ⁱ	144	0.9 [0.7; 1.6] 134 (93.1)	142	1.5 [1.0; 2.1] 126 (88.7)	1.05 [0.82; 1.36]; 0.686
Discontinuation due to AEs	144	NA [44.3; NC] 63 (43.8)	142	44.2 [26.5; NC] 68 (47.9)	0.76 [0.54; 1.07]; 0.115
Peripheral neuropathy (HLT, severe AEs ⁱ)	144	NA 18 (12.5)	142	NA 16 (11.3)	1.12 [0.57; 2.21]; 0.735
a. Followed by treatment with daratumumab + lenalidomide + dexamethasone in Cycle 9 and beyond. b. Followed by treatment with lenalidomide + dexamethasone in Cycle 9 and beyond. c. Effect, CI and p-value according to information provided by the company: Cox proportional hazards model; each stratified according to ISS stage (I vs. II vs. III) and age/ASCT eligibility (≥ 70 years vs. < 70 years ASCT ineligible vs. < 70 years and refusal to have ASCT). Patients < 70 years who had refused ASCT were not included in the subpopulation relevant for the benefit assessment, which was analysed here. d. A score increase in EORTC QLQ-C30 and EORTC QLQ-MY20 by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100). e. According to Module 4 A, only patients with a baseline value and at least one other value in the course of the study are included in the analyses. f. Institute's calculation. g. An EQ-5D VAS score decrease by ≥ 15 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100). h. A score decrease in EORTC QLQ-C30 and EORTC QLQ-MY20 by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100). i. Operationalized as CTCAE grade ≥ 3. AE: adverse event; ASCT: autologous stem cell transplantation; 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; ISS: International Staging System; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Myeloma Module 20; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale					

Based on the available information, at most hints, e.g. of an added benefit, could be determined for all outcomes (for reasoning, see Sections I 3.2. and I 4.2).

Mortality

Overall survival

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

Morbidity

Symptoms (recorded with the EORTC QLQ-C30)

Fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, and diarrhoea

No statistically significant difference between the treatment arms was shown for any of the outcomes of fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, and diarrhoea. There was no hint of an added benefit of daratumumab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone for any of the outcomes; an added benefit is therefore not proven in each case.

Constipation

A statistically significant difference in favour of daratumumab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone was shown for the outcome constipation. However, the difference is no more than marginal for this outcome in the category of non-serious/non-severe symptoms/late complications. There was no hint of an added benefit of daratumumab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone; an added benefit is therefore not proven.

Symptoms (recorded with the EORTC QLQ-MY20)

Disease symptoms and side effects

There was no statistically significant difference between the treatment arms for either of the outcomes disease symptoms and side effects. There was no hint of an added benefit of daratumumab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone for any of the outcomes; an added benefit is therefore not proven in each case.

Health status (recorded using the EQ-5D VAS)

No statistically significant difference between the treatment arms was shown for the outcome health status, recorded using the EQ-5D VAS. There was no hint of an added benefit of daratumumab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone; an added benefit is therefore not proven.

Health-related quality of life***EORTC QLQ-C30***

No statistically significant difference between the treatment arms was shown for any of the outcomes global health status, physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning. There was no hint of an added benefit of daratumumab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone for any of the outcomes; an added benefit is therefore not proven in each case.

EORTC QLQ-MY20

No statistically significant difference between the treatment arms was shown for the outcomes of future perspective and body image. There was no hint of an added benefit of daratumumab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone for any of the outcomes; an added benefit is therefore not proven in each case.

Side effects***SAEs, severe AEs, and discontinuation due to AEs***

There was no statistically significant difference between treatment arms for either of the outcomes of SAEs, severe AEs or discontinuation due to AEs. There was no hint of greater or lesser harm of daratumumab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone for any of the outcomes; greater or lesser harm is therefore not proven in each case.

Peripheral neuropathy (severe AEs)

There was no statistically significant difference between the treatment arms for the outcome peripheral neuropathy (severe AEs). There was no hint of greater or lesser harm of daratumumab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone; greater or lesser harm is therefore not proven.

I 4.4 Subgroups and other effect modifiers

No subgroup analyses for the CEPHEUS study were used as part of the benefit assessment. The reasons for this are as follows:

The CEPHEUS study was relevant for the given research question. However, with regard to the relevant subpopulation included (patients ineligible for ASCT), the results were subject to uncertainty (see Section I 3.2). For downstream subgroup analyses, this resulted in the following additional uncertainty: It is unknown how patients who were still eligible for ASCT were distributed across possible subgroups and to what extent this would lead to a bias in the subgroup results. The results from the subgroup analyses were therefore assessed as non-interpretable, and no subgroup analyses were used for this benefit assessment.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG General Methods [1].

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

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Chapter I 4 (see Table 16).

Determination of the outcome category for symptom outcomes

It cannot be inferred from the dossier whether the following symptoms outcome is serious/severe or non-serious/non-severe. The classification of this outcome is explained below.

Constipation (EORTC QLQ-C30)

For the outcome constipation (EORTC QLQ-C30), insufficient severity data were available for a classification as serious/severe. The outcome of constipation (EORTC QLQ-C30) was therefore allocated to the outcome category of non-serious/non-severe symptoms/late complications.

Table 16: Extent of added benefit at outcome level: daratumumab + bortezomib + lenalidomide + dexamethasone^a vs. bortezomib + lenalidomide + dexamethasone^b (multipage table)

Outcome category Outcome	daratumumab + bortezomib + lenalidomide + dexamethasone ^a vs. bortezomib + lenalidomide + dexamethasone ^b Median time to event (months) Effect estimation [95% CI]; p-value Probability ^c	Derivation of extent ^d
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	NA vs. NA HR: 0.66 [0.42; 1.03]; p = 0.070	Lesser benefit not proven / added benefit not proven
Morbidity		
Health status (time to first deterioration by ≥ 15 points)		
EQ-5D VAS	4.2 vs. 6.5 HR: 1.14 [0.81; 1.60]; p = 0.450	Lesser benefit not proven / added benefit not proven
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30 – time to first deterioration by ≥ 10 points)		
Fatigue	1.5 vs. 1.5 HR: 1.09 [0.82; 1.45]; p = 0.569	Lesser benefit not proven / added benefit not proven
Nausea and vomiting	6.0 vs. 11.4 HR: 1.22 [0.88; 1.69]; p = 0.232	Lesser benefit not proven / added benefit not proven
Pain	3.7 vs. 3.5 HR: 0.91 [0.67; 1.24]; p = 0.549	Lesser benefit not proven / added benefit not proven
Dyspnoea	3.1 vs. 5.3 HR: 1.24 [0.93; 1.66]; p = 0.152	Lesser benefit not proven / added benefit not proven
Insomnia	2.8 vs. 2.8 HR: 1.03 [0.77; 1.38]; p = 0.834	Lesser benefit not proven / added benefit not proven
Appetite loss	4.3 vs. 3.6 HR: 0.94 [0.70; 1.24]; p = 0.644	Lesser benefit not proven / added benefit not proven

Table 16: Extent of added benefit at outcome level: daratumumab + bortezomib + lenalidomide + dexamethasone^a vs. bortezomib + lenalidomide + dexamethasone^b (multipage table)

Outcome category Outcome	daratumumab + bortezomib + lenalidomide + dexamethasone ^a vs. bortezomib + lenalidomide + dexamethasone ^b Median time to event (months) Effect estimation [95% CI]; p-value Probability ^c	Derivation of extent ^d
Constipation	3.1 vs. 1.6 HR: 0.69 [0.51; 0.92]; p = 0.011	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Lesser benefit not proven / added benefit not proven ^e
Diarrhoea	4.7 vs. 3.7 HR: 0.88 [0.67; 1.16]; p = 0.368	Lesser benefit not proven / added benefit not proven
Symptoms (EORTC QLQ-MY20 – time to first deterioration by ≥ 10 points)		
Disease symptoms	11.6 vs. 13.9 HR: 1.09 [0.78; 1.52]; p = 0.619	Lesser benefit not proven / added benefit not proven
Side effects	2.4 vs. 2.9 HR: 1.19 [0.88; 1.59]; p = 0.255	Lesser benefit not proven / added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 (time to first deterioration by ≥ 10 points)		
Global health status	2.1 vs. 2.8 HR: 1.19 [0.87; 1.63]; p = 0.276	Lesser benefit not proven / added benefit not proven
Physical functioning	3.0 vs. 3.5 HR: 1.10 [0.82; 1.49]; p = 0.526	Lesser benefit not proven / added benefit not proven
Role functioning	2.1 vs. 2.8 HR: 1.04 [0.77; 1.41]; p = 0.788	Lesser benefit not proven / added benefit not proven
Emotional functioning	9.3 vs. 5.3 HR: 0.89 [0.64; 1.23]; p = 0.466	Lesser benefit not proven / added benefit not proven
Cognitive functioning	2.6 vs. 3.5 HR: 1.18 [0.89; 1.56]; p = 0.260	Lesser benefit not proven / added benefit not proven

Table 16: Extent of added benefit at outcome level: daratumumab + bortezomib + lenalidomide + dexamethasone^a vs. bortezomib + lenalidomide + dexamethasone^b (multipage table)

Outcome category Outcome	daratumumab + bortezomib + lenalidomide + dexamethasone ^a vs. bortezomib + lenalidomide + dexamethasone ^b Median time to event (months) Effect estimation [95% CI]; p-value Probability ^c	Derivation of extent ^d
Social functioning	2.8 vs. 2.6 HR: 0.98 [0.73; 1.32]; p = 0.889	Lesser benefit not proven / added benefit not proven
EORTC QLQ-MY20 (time to first deterioration by ≥ 10 points)		
Future perspective	8.4 vs. 13.7 HR: 1.03 [0.74; 1.45]; p = 0.844	Lesser benefit not proven / added benefit not proven
Body image	8.8 vs. 11.6 HR: 1.29 [0.93; 1.80]; p = 0.133	Lesser benefit not proven / added benefit not proven
Side effects		
SAEs	12.3 vs. 8.3 HR: 0.93 [0.70; 1.23]; p = 0.600	Greater/lesser harm not proven
Severe AEs	0.9 vs. 1.5 HR: 1.05 [0.82; 1.36]; p = 0.686	Greater/lesser harm not proven
Discontinuation due to AEs	NA vs. 44.2 HR: 0.76 [0.54; 1.07]; p = 0.115	Greater/lesser harm not proven
Peripheral neuropathy (severe AEs)	NA vs. NA HR: 1.12 [0.57; 2.21]; p = 0.735	Greater/lesser harm not proven
a. Followed by treatment with daratumumab + lenalidomide + dexamethasone in Cycle 9 and beyond. b. Followed by treatment with lenalidomide + dexamethasone in Cycle 9 and beyond. c. Probability provided if there is a statistically significant and relevant effect. d. Estimates of the effect size are made with different limits depending on the outcome category using the upper limit of the confidence interval (CI_u). e. The extent of the effect in this non-serious/non-severe outcome was no more than marginal. AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; NA: not achieved; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma 20; SAE: serious adverse event; VAS: visual analogue scale		

I 5.2 Overall conclusion on added benefit

Table 17 summarizes the results taken into account for the overall conclusion on the extent of the added benefit.

Table 17: Positive and negative effects from the assessment of daratumumab + bortezomib + lenalidomide + dexamethasone^a in comparison with bortezomib + lenalidomide + dexamethasone^b

Positive effects	Negative effects
–	–
a. Followed by treatment with daratumumab + lenalidomide + dexamethasone in Cycle 9 and beyond. b. Followed by treatment with lenalidomide + dexamethasone in Cycle 9 and beyond.	

Neither positive nor negative effects were found for daratumumab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone.

In summary, there is no hint of an added benefit of daratumumab + bortezomib + lenalidomide + dexamethasone versus bortezomib + lenalidomide + dexamethasone for adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant; an added benefit is therefore not proven.

Table 18 summarizes the result of the assessment of the added benefit of daratumumab + bortezomib + lenalidomide + dexamethasone in comparison with the ACT.

Table 18: Daratumumab + bortezomib + lenalidomide + dexamethasone – probability and extent of added benefit

Therapeutic indication	ACT ^a	Probability and extent of added benefit
Adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant	▪ daratumumab in combination with lenalidomide and dexamethasone or ▪ daratumumab in combination with bortezomib, melphalan and prednisone or ▪ bortezomib in combination with melphalan and prednisone or ▪ bortezomib in combination with lenalidomide and dexamethasone or ▪ thalidomide in combination with melphalan and prednisone or ▪ bortezomib in combination with cyclophosphamide and dexamethasone (only for patients with peripheral polyneuropathy or an increased risk of developing peripheral polyneuropathy^b)	Added benefit not proven
a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company according to the inclusion criteria in Module 4 Section 4.2.2 is printed in bold. b. See Appendix VI to Section K of the Pharmaceutical Directive. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The assessment described above deviates from that of the company, which, based on the results of the CEPHEUS study, derived a hint of a considerable added benefit of daratumumab + bortezomib + lenalidomide + dexamethasone versus the ACT for adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.

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

I 6 References for English extract

Please see full dossier assessment for full reference list.

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

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 7.0 [online]. 2023 [Accessed: 16.10.2025]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.pdf.
2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. *Biom J* 2016; 58(1): 43-58. <https://doi.org/10.1002/bimj.201300274>.
3. Janssen Research & Development. A Phase 3 Study Comparing Daratumumab, VELCADE (bortezomib), Lenalidomide, and Dexamethasone (D-VRd) with VELCADE, Lenalidomide, and Dexamethasone (VRd) in Subjects with Untreated Multiple Myeloma and for Whom Hematopoietic Stem Cell Transplant is Not Planned as Initial Therapy; study CEPHEUS; Clinical Study Report [unpublished]. 2024.
4. Janssen Research & Development. A Phase 3 Study Comparing Daratumumab, VELCADE (bortezomib), Lenalidomide, and Dexamethasone (D-VRd) with VELCADE, Lenalidomide, and Dexamethasone (VRd) in Subjects with Untreated Multiple Myeloma and for Whom Hematopoietic Stem Cell Transplant is Not Planned as Initial Therapy; study CEPHEUS; Zusatzanalysen [unpublished]. 2025.
5. Janssen - Cilag International. A Phase 3 Study Comparing Daratumumab, VELCADE (bortezomib), Lenalidomide, and Dexamethasone (D-VRd) with VELCADE, Lenalidomide, and Dexamethasone (VRd) in Subjects with Untreated Multiple Myeloma and for Whom Hematopoietic Stem Cell Transplant is Not Planned as Initial Therapy [online]. 2025 [Accessed: 13.10.2025]. URL: <https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2023-507312-13-00>.
6. Janssen Research & Development. A Study Comparing Daratumumab, VELCADE (Bortezomib), Lenalidomide, and Dexamethasone (D-VRd) With VELCADE, Lenalidomide, and Dexamethasone (VRd) in Participants With Untreated Multiple Myeloma and for Whom Hematopoietic Stem Cell Transplant is Not Planned as Initial Therapy [online]. 2025 [Accessed: 13.10.2025]. URL: <https://clinicaltrials.gov/study/NCT03652064>.

7. Janssen-Cilag International. A Phase 3 Study Comparing Daratumumab, VELCADE (bortezomib), Lenalidomide, and Dexamethasone (D-VRd) with VELCADE, Lenalidomide, and Dexamethasone (VRd) in Subjects with Untreated Multiple Myeloma and for Whom Hematopoietic Stem Cell Transplant is Not Planned as Initial Therapy [online]. [Accessed: 13.10.2025]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2018-001545-13.
8. Usmani SZ, Facon T, Hungria V et al. Daratumumab plus bortezomib, lenalidomide and dexamethasone for transplant-ineligible or transplant-deferred newly diagnosed multiple myeloma: the randomized phase 3 CEPHEUS trial. Nat Med 2025; 31(4): 1195-1202. <https://doi.org/10.1038/s41591-024-03485-7>.
9. Usmani SZ, Facon T, Hungria V et al. Author Correction: Daratumumab plus bortezomib, lenalidomide and dexamethasone for transplant-ineligible or transplant-deferred newly diagnosed multiple myeloma: the randomized phase 3 CEPHEUS trial. Nat Med 2025; 31(4): 1366. <https://doi.org/10.1038/s41591-025-03581-2>.
10. TAD Pharma. Dexamethason TAD 20 mg/ - 40 mg Tabletten [online]. 01.2022 [Accessed: 29.08.2025]. URL: <https://portal.cgmlauer.cgm.com/LF/default.aspx?p=12000>.
11. Stragen. Lenalidomid OHRE Pharma [online]. 10.2022 [Accessed: 16.10.2025]. URL: <https://www.fachinfo.de>.
12. medac. Bortezomib medac 2,5 mg Pulver zur Herstellung einer Injektionslösung [online]. 04.2025 [Accessed: 16.10.2025]. URL: <https://www.fachinfo.de>.
13. Johnson & Johnson. DARZALEX 1 800 mg Injektionslösung [online]. 07.2025 [Accessed: 16.10.2025]. URL: <https://www.fachinfo.de>.
14. European Medicines Agency. Darzalex; Assessment report [online]. 2025 [Accessed: 30.10.2025]. URL: https://www.ema.europa.eu/en/documents/variation-report/darzalex-h-c-004077-ii-0076-epar-assessment-report-variation_en.pdf.
15. Kortüm M, Auner HW, Bassermann F et al. Multiples Myelom [online]. 2024 [Accessed: 16.10.2025]. URL: <https://www.onkopedia.com/de/onkopedia/guidelines/multiples-myelom/@@guideline/html/index.html>.
16. Leitlinienprogramm Onkologie. S3-Leitlinie Diagnostik, Therapie und Nachsorge für Patienten mit monoklonaler Gammopathie unklarer Signifikanz (MGUS) oder Multiplem Myelom [online]. 2022 [Accessed: 16.10.2025]. URL: https://register.awmf.org/assets/guidelines/018-0350LI_S3_Diagnostik-Therapie-Nachsorge-monoklonaler-Gammopathie-unklarer-Signifikanz-MGUS-Multiplem-Myelom_2022-05.pdf.

17. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Daratumumab (multiples Myelom) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2018 [Accessed: 16.10.2025]. URL: https://www.iqwig.de/download/a18-66_daratumumab_nutzenbewertung-35a-sgb-v_v1-0.pdf.
18. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Daratumumab (multiples Myelom); Nutzenbewertung gemäß § 35a SGB V (Ablauf Befristung); Dossierbewertung [online]. 2024 [Accessed: 16.10.2025]. URL: <https://doi.org/10.60584/A23-127>.
19. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Isatuximab (multiples Myelom); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2025 [Accessed: 16.10.2025]. URL: https://doi.org/10.60584/A25-20_V1.1.
20. Dimopoulos MA, Terpos E, Boccadoro M et al. EHA-EMN Evidence-Based Guidelines for diagnosis, treatment and follow-up of patients with multiple myeloma. Nat Rev Clin Oncol 2025; 22(9): 680-700. <https://doi.org/10.1038/s41571-025-01041-x>.
21. G. B. A. Gemeinsamer Bundesausschuss. Mündliche Anhörung gemäß § 35 a Abs. 3 Satz 2 SGB V des Gemeinsamen Bundesausschusses hier: Isatuximab (D-1140) [online]. 2025 [Accessed: 15.07.2025]. URL: https://www.g-ba.de/downloads/91-1031-1174/2025-06-23_Wortprotokoll_Isatuximab_D-1140.pdf.

The full report (German version) is published at
<https://www.iqwig.de/en/projects/a25-108.html>.