IQWiG Reports – Commission No. A20-14

Daratumumab (newly diagnosed multiple myeloma, stem cell transplant unsuitable) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Daratumumab (neu diagnostiziertes multiples Myelom, Stammzelltransplantation nicht geeignet) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 May 2020). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ASCT	autologous stem cell transplantation
CTCAE	Common Terminology Criteria for Adverse Events
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EQ-5D VAS	European Quality of Life Questionnaire – 5 Dimensions Visual Analogue Scale
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
ISS	International Staging System
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PFS	progression-free survival
PT	preferred term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
SOC	System Organ Class
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Extract of dossier assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug daratumumab (in combination with lenalidomide and dexamethasone). The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 17 February 2020.

Research question

The aim of the present report was to assess the added benefit of daratumumab in combination with lenalidomide and dexamethasone in comparison with the appropriate comparator therapy (ACT) for adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplantation (ASCT).

The ACT specified by the G-BA is presented in Table 2.

Table 2: Research questions of the benefit assessment of daratumumab

Therapeutic indication	**ACT**[a]
Daratumumab in combination with lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for stem cell transplantation	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 **Lenalidomide in combination with dexamethasone**
a. Presentation of the respective 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 by the company is printed in **bold**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA's specification of the ACT. From the options named by the G-BA, the company selected lenalidomide in combination with dexamethasone.

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

Results

Study pool and study characteristics

The study pool for the benefit assessment consisted of the MAIA study. This study is an open-label, randomized, actively controlled trial directly comparing daratumumab + lenalidomide + dexamethasone versus lenalidomide + dexamethasone. The study is still ongoing. It included adults (≥ 18 years of age) with newly diagnosed multiple myeloma who were ineligible for high-dose chemotherapy with subsequent ASCT. Patients additionally had to have an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0 to 2 as a measure of general health. In accordance with the inclusion criteria, patients were considered ineligible for ASCT if they were age 65 years or older or if they were under 65 years and had relevant comorbidities. Since eligibility for ASCT was not determined on an individual patient level, patients who would in fact have been eligible for ASCT might have been included in the study.

A total of 737 patients were randomly allocated to the study arms, of which 368 were in the intervention arm receiving daratumumab + lenalidomide + dexamethasone and 369 in the control arm receiving lenalidomide + dexamethasone.

In both study arms, treatment was administered in 4-week cycles until disease progression, unacceptable toxicity, withdrawal of consent, or study end. The drugs were used largely in accordance with the specifications of the Summaries of Product Characteristics (SPCs). Patients discontinuing any component of the treatment regimen were allowed to continue treatment with the remaining components of their regimen.

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

Due to the MAIA study's uncertainty regarding the unknown percentage of patients who were in fact eligible for ASCT, at most hints, e.g. of an added benefit, can be derived from it.

Risk of bias at study and outcome levels

The risk of bias across outcomes was rated as low in the MAIA study. At the outcome level, the results are rated as highly biased for every outcome except overall survival and severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3). No usable data are available for the outcomes of discontinuation due to AEs and infusion-related reaction.

Results

Mortality: Overall survival

For the outcome of overall survival, no statistically significant difference between treatment groups was found. Consequently, there is no hint of added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone; an added benefit is therefore not proven.

Morbidity: Health status (European Quality of Life Questionnaire – 5 Dimensions Visual Analogue Scale [EQ-5D VAS])

For the outcome of health status as measured by EQ-5D VAS, mean value comparisons show a statistically significant difference between treatment arms for the available data cut-off date of 24 September 2018. To check the relevance of the result, the standardized mean difference (SMD) was considered in the form of Hedges' g. The 95% confidence interval of the SMD in the form of Hedges' g is not fully outside of the irrelevance range of −0.2 to 0.2. Hence, the effect cannot be rated as relevant. Consequently, there is no hint of added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone; an added benefit is therefore not proven.

Morbidity: Symptoms (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Cancer30 [EORTC QLQ-C30] – symptom scales)

In each case, time to deterioration by ≥ 10 points was the criterion. For the pain scale, a statistically significant difference was found in favour of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone. Consequently, there is a hint of added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone.

For the dyspnoea scale, a statistically significant difference was found in favour of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone. The difference, however, is no more than marginal for this outcome in the category of non-serious/non-severe symptoms/late complications. This does not result in a hint of added benefit; an added benefit is therefore not proven for this outcome.

For each of the outcomes of fatigue, nausea and vomiting, insomnia, appetite loss, constipation, and diarrhoea, no statistically significant difference between treatment arms was found. For each of these outcomes, there is consequently no hint of added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone; an added benefit is therefore not proven for these outcomes.

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

In each case, time to deterioration by ≥ 10 points was the criterion. For each of the outcomes of physical functioning and social functioning, a statistically significant difference was found in favour of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone. Consequently, for each of these two outcomes, there is a hint of added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone.

For each of the outcomes of global health status, role functioning, emotional functioning, and cognitive functioning, no statistically significant difference between treatment arms was found. For each of these outcomes, there is consequently no hint of added benefit of daratumumab +

lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone; an added benefit is therefore not proven for these outcomes.

Adverse events

For the outcome of serious AEs (SAEs), no statistically significant difference between treatment arms was found. Consequently, there is no hint of greater or lesser harm of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone; greater or lesser harm is therefore not proven.

For the outcome of severe AEs (CTCAE grade ≥ 3), a statistically significant difference to the disadvantage of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone was found. Consequently, there is a hint of greater harm of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone.

No usable data are available for the outcomes of discontinuation due to AEs and infusion-related reaction.

For the outcomes of skin and subcutaneous tissue disorders (System Organ Class [SOC], CTCAE grade ≥ 3) and anaemia (preferred term [PT], CTCAE grade ≥ 3), a statistically significant difference in favour of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone was found. Consequently, these 2 specific AEs provide a hint of lesser harm of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone. However, it is questionable whether the effect on the outcome of anaemia (PT, CTCAE grade ≥ 3) is actually attributable to the outcome category of adverse events or whether it rather reflects the clinical picture of the underlying disease.

For each of the outcomes of chills (PT, AEs), respiratory, thoracic, and mediastinal disorders (SOC, AEs), infections and infestations (SOC, SAEs), and neutropenia (PT, CTCAE grade ≥ 3), a statistically significant difference was found to the disadvantage of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone. Consequently, for each of these 4 specific AEs, there is a hint of greater harm of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone.

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

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

All things considered, both positive and negative effects of different extents were found for daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone. Negative effects concern exclusively AE outcomes (4 specific AEs, most with effects of considerable extent, and total rate of severe AEs (CTCAE grade ≥ 3), with effects of considerable extent). Positive effects were of considerable extent for 2 specific AEs and of minor extent for pain as a symptom and for 2 of 6 health-related quality of life scales. All things considered, positive and negative effects are deemed balanced.

In summary, there is no proof of added benefit of daratumumab in combination with lenalidomide and dexamethasone in comparison with lenalidomide and dexamethasone for adult patients with newly diagnosed multiple myeloma who are ineligible for ASCT.

Table 3 presents a summary of the probability and extent of added benefit of daratumumab in combination with lenalidomide and dexamethasone in comparison with the ACT.

[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 – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Daratumumab in combination with lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for stem cell transplantation	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 **Lenalidomide in combination with dexamethasone**	Added benefit not proven

a. Presentation of the respective 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 by the company is printed in **bold**.

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

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

2.2 Research question

The aim of the present report was to assess the added benefit of daratumumab in combination with lenalidomide and dexamethasone in comparison with the ACT for adult patients with newly diagnosed multiple myeloma who are ineligible for ASCT.

The ACT specified by the G-BA is presented in Table 4.

Table 4: Research questions of the benefit assessment of daratumumab

Therapeutic indication	**ACT**[a]
Daratumumab in combination with lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for stem cell transplantation	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 **Lenalidomide in combination with dexamethasone**
a. Presentation of the respective 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 by the company is printed in **bold**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA's specification of the ACT. From the options mentioned by the G-BA, the company selected lenalidomide in combination with dexamethasone.

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

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- Study list on daratumumab (status: 15 January 2020)
- Bibliographic literature search on daratumumab (most recent search on 15 January 2020)
- Search in trial registries / study results databases on daratumumab (most recent search on 15 January 2020)
- Search on the G-BA website on daratumumab (most recent search on 15 January 2020)

To check the completeness of the study pool:

- Search in trial registries for studies on daratumumab (most recent search on 02 March 2020)

The check did not identify any additional relevant studies.

2.3.1 Included studies

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

Table 5: Study pool – RCT, direct comparison: daratumumab + lenalidomide + dexamethasone versus lenalidomide + dexamethasone

Study	Study category			Available sources		
	Approval study for the drug to be assessed (Yes/No)	Sponsored study[a] (Yes/No)	Third-party study (Yes/No)	Clinical study report (Yes/No [reference])	Registry entries[b] (Yes/No [reference])	Publication (Yes/No [reference])
54767414MMY 3008 (MAIA[c])	Yes	Yes	No	Yes [3-5]	Yes [6-8]	Yes [9]

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to by this short name.

RCT: randomized controlled trial

The study pool for the benefit assessment includes the MAIA study comparing daratumumab + lenalidomide + dexamethasone versus lenalidomide + dexamethasone.

Alongside the MAIA study, the company's study pool includes the ALCYONE study, which the company presents as supplementary evidence as part of a metaanalysis of the MAIA and ALCYONE studies. In the ALCYONE study, daratumumab in combination with bortezomib, melphalan, and prednisone is compared with bortezomib in combination with melphalan and prednisone. In the given therapeutic indication, both drug combinations of the two treatment arms are considered ACTs. Further, some of the combination partners of daratumumab are in drug classes other than those intended for the therapeutic indication. Lenalidomide, which is intended for the present therapeutic indication, is an immunomodulator. In contrast, the combination drugs in the ALCYONE study include a proteasome inhibitor (bortezomib) and a cytostatic drug (melphalan). Only dexamethasone (therapeutic indication) and prednisone (ALCYONE study) are in the same drug class of glucocorticoids. Overall, the ALCYONE study is therefore unsuitable for answering the present research question to assess any added benefit of daratumumab in combination with lenalidomide and dexamethasone, and it was not used for the benefit assessment. The benefit assessment of daratumumab in combination with bortezomib, melphalan, and prednisone is the subject of dossier assessment A18-66 [10].

The company presented the results of the ALCYONE study as supplementary evidence as part of a metaanalysis of the MAIA and ALCYONE studies, but it did not use them to assess any added benefit.

Suitability of autologous stem cell transplantation for the study population

For the MAIA study, it is unclear whether the included patients were in fact ineligible for high-dose chemotherapy with subsequent ASCT, as intended in the therapeutic indication. According to the study's inclusion criteria, ASCT was considered unsuitable for patients under 65 years of age with relevant comorbidities as well as for patients 65 years of age or older. At the time the study was planned, these criteria were appropriate for operationalizing the absence of a therapeutic indication for ASCT. Over the course of the study, however, the criteria for assessing patient eligibility for ASCT changed. Since then, biological age and good general health have been considered more important than chronological age [11-14]. It is difficult to define a maximum age for ASCT therapy. Rather, the eligibility for ASCT is to be assessed individually for each patient, taking into account general health, any comorbidities, and organ function.

Consequently, taking into account current guidelines, it is inappropriate to consider patients ineligible for ASCT based solely on their chronological age (≥ 65 years), as was done in the MAIA study. The defined inclusion criterion of age ≥ 65 years (without further consideration of general health) might mean that patients who would have been eligible for ASCT were included in the study; these patients do not represent the population of the therapeutic indication to be assessed. Additional data (AEs) were also requested by the European Medicines Agency (EMA) as part of the marketing authorization procedure. These data referred to 1 post hoc defined subpopulation, whose characteristics largely suggest that ASCT is not a suitable treatment option: ≥ 75 years of age and 65 to 74 years of age with relevant comorbidities and/or fair general health (e.g. Eastern Cooperative Oncology Group Performance Status [ECOG-PS] = 2) [15]. In response, the company defined post hoc the following 2 subpopulations as part of the marketing authorization procedure:

- Subpopulation 1
  - Age < 65 years with relevant comorbidities or
  - Age 65 to 69 years with ECOG-PS = 2 or
  - Age ≥ 70 years
- Subpopulation 2
  - Age < 65 years with relevant comorbidities or ECOG-PS = 2 or
  - Age 65 to 74 years with ECOG-PS = 2 or
  - Age ≥ 75 years

Populations presented by the company

Similar to the dossier for the assessment of daratumumab in combination with bortezomib, melphalan, and prednisone [16] as well as the dossier for the present assessment, the company likewise presented data on the above-defined subpopulation 1 for the MAIA study (below referred to as the "ASCT-ineligible" subpopulation in accordance with the company's designation). This population comprises 305 patients in the intervention arm and 307 patients in the comparator arm (each corresponding to 83% of the total population). For deriving an added benefit, the company uses the results of the total population of the MAIA study. The company considers the "ASCT-ineligible" subpopulation in the context of subgroup analyses. In particular, the company justifies this approach by stating that the results of the total population are comparable to those of the subpopulation, and furthermore, no difference in effects were found in the subgroup analysis ("ASCT eligible" versus "ASCT ineligible"). In addition, the company uses analyses of German health services data to investigate whether the study population should still be considered ineligible for ASCT according to current criteria [17,18]. On the basis of these data, the company concludes that the proportion of the MAIA study population who might in fact be eligible for ASCT is about 6% to 15%.

The company's approach for operationalizing the "ASCT-ineligible" subpopulation is plausible. Nevertheless, both the subpopulation and the total population are subject to uncertainty. Regarding the definition of the population ineligible for ASCT, the uncertainty is underscored by the fact that data for 2 subpopulations with different ASCT ineligibility criteria were considered in the marketing authorization procedure (see above). According to guideline recommendations, ineligibility for ASCT should be determined on individually for each patient without regard to chronological age. This was not done in this form in the MAIA study, and it is impossible to gather the corresponding data post hoc (e.g. due to lack of comorbidity data). However, a comparison of the results of the "ASCT-ineligible" subpopulation (see Appendix D of the full dossier assessment) with those of the total population shows that the effect size is very similar for each of the outcomes relevant for the decision. The EMA as well bases its recommendation for approval only on the overall population [19]. Analogously to the company's approach, the benefit assessment was therefore conducted on the basis of the results of the total population, with supplementary presentation of the results of the "ASCT-ineligible" subpopulation. However, the uncertainty in the form of the unknown percentage of patients for whom ASCT represents a potential treatment option over the course of therapy means that at most hints, e.g. of added benefit, can be derived. In the sections below, characteristics and results are presented only for the total population. The results for the subpopulation (ASCT ineligible) are presented as supplementary information in Appendix D of the full dossier assessment.

2.3.2 Study characteristics

Table 6 and Table 7 present the study used in the benefit assessment.

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and time period conducted	Primary outcome; secondary outcomes[a]
MAIA	RCT, open-label, parallel-group	Adults (≥ 18 years of age) with newly diagnosed multiple myeloma, ▪ who are ineligible for high-dose chemotherapy with autologous stem cell transplantation (≥ 65 years of age or, in the presence of relevant comorbidities, < 65 years of age) ▪ ECOG-PS ≤ 2	Daratumumab + lenalidomide + dexamethasone (N = 368) Lenalidomide + dexamethasone (N = 369)	Screening: ≤ 21 days before randomization Treatment: Until disease progression, unacceptable toxicity, withdrawal of consent, or study end[b] Follow-up observation[c]: Outcome-specific; at the longest until either death, withdrawal of consent, or study end[b]	176 study centres in Australia, Austria, Belgium, Canada, Denmark, France, Germany, Ireland, Israel, Italy, Netherlands, Sweden, United Kingdom, USA 03/2015–ongoing 1st data cut-off date: 24/09/2018 2nd data cut-off date: 10/06/2019	Primary: PFS Secondary: Overall survival, health status, symptoms, health-related quality of life, AEs

a. Primary outcomes include information without consideration of relevance for this benefit assessment. Secondary outcomes include only information on available outcomes relevant for this benefit assessment.
b. The study ends after 330 deaths or 7 years after the last patient was randomized.
c. Outcome-specific information is provided in Table 8. Patients who discontinue treatment before progression of disease are followed up until confirmed disease progression, subsequent anti-myeloma therapy, withdrawal of consent, lost to follow-up, study end, or death.

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

Table 7: Characterization of the intervention – RCT, direct comparison: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone (multi-page table)

Study	Intervention	Comparison
MAIA	Daratumumab: 16 mg/kg body weight i.v. ▪ Cycles 1–2: weekly (Days 1, 8, 15, 22) ▪ Cycles 3–6: every 2 weeks (Days 1, 15) ▪ From cycle 7: every 4 weeks (Day 1) + Lenalidomide: from Cycle 1, daily (Days 1–21) ▪ 25 mg orally at a creatinine clearance > 50 mL/min ▪ 10 mg orally at a creatinine clearance 30–50 mL/min + Dexamethasone: from Cycle 1: weekly (Days 1, 8, 15, 22) ▪ 40 mg/week in patients ≤ 75 years of age ▪ 20 mg/week in patients > 75 years of age or patients with a BMI < 18.5 Each cycle corresponds to 4 weeks	Lenalidomide: from Cycle 1, daily (Days 1–21) ▪ 25 mg orally at a creatinine clearance > 50 mL/min ▪ 10 mg orally at a creatinine clearance 30–50 mL/min + Dexamethasone: from Cycle 1: weekly (Days 1, 8, 15, 22) ▪ 40 mg/week in patients ≤ 75 years of age ▪ 20 mg/week in patients > 75 years of age or patients with a BMI < 18.5 Each cycle corresponds to 4 weeks
	Treatment modifications ▪ Daratumumab: Dose modifications are not allowed[a] ▪ Lenalidomide, dexamethasone: In accordance with the study protocol, dose reduction or drug discontinuation was allowed[b] ▪ Patients who discontinue a single component of their treatment regimens are allowed to continue the treatment with the remaining components.	
	Premedication and postmedication of daratumumab	
	Premedication before daratumumab ▪ Paracetamol 650–1000 mg i.v. or orally ▪ Antihistamine (diphenhydramine 25–50 mg i.v. or orally, or an equivalent with the exception of promethazine) **Postmedication after daratumumab** For patients at increased risk of respiratory complications (e.g. mild asthma), the following drugs were to be considered after the infusion: ▪ Antihistamine (diphenhydramine or an equivalent) ▪ Short-acting beta-2 sympathomimetic (e.g. salbutamol) ▪ Medication to control the respective respiratory disease (e.g. inhaled corticosteroids, long-acting bronchodilators)	

Table 7: Characterization of the intervention – RCT, direct comparison: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone (multi-page table)

Study	Intervention	Comparison
	Concomitant treatment	
	Allowed ▪ During the study, all drugs and therapies considered necessary for supportive therapy were allowed (exception: disallowed concomitant treatments, see below)	
	Recommended ▪ Thrombosis prophylaxis: ▫ Depending on risk factors: Acetylsalicylic acid, low-molecular weight heparin, or warfarin ▪ Bisphosphonates (continuation of existing therapy; treatment start allowed only until the end of the Cycle 1) ▪ Therapy for tumour lysis syndrome ▪ Infection prophylaxis (e.g. *Pneumocystis carinii prophylaxis*, *herpes zoster* prevention)	
	Disallowed ▪ Other antineoplastic myeloma therapy ▪ Systemic corticosteroids (> 10 mg prednisone/day or equivalent) – except in case of infusion-related AEs – and NSAIDS should be given with caution	

a. In case of infusion-related reactions, the infusion is paused until stabilization, the infusion speed is adjusted, or the treatment discontinued, depending on severity.
b. Toxicity-related dose modifications or even treatment discontinuation were conducted without relevant deviations from the requirements in the Summary of Product Characteristics.

BMI: body mass index; i.v.: intravenous; NSAID: non-steroidal anti-inflammatory drug; RCT: randomized controlled trial

The MAIA study is an open-label, randomized, actively controlled study for the direct comparison of daratumumab + lenalidomide + dexamethasone versus lenalidomide + dexamethasone. The study is still ongoing.

The study included adults (≥ 18 years of age) with newly diagnosed multiple myeloma who were ineligible for high-dose chemotherapy with subsequent ASCT. Patients also had to be in a general condition corresponding to an ECOG-PS of 0 to 2. In accordance with the inclusion criteria, patients were considered ineligible for ASCT if they were either 65 years of age or older or were less than 65 years of age and had relevant comorbidities. Since the eligibility for ASCT was not determined individually for each patient, it is possible for patients who would in fact have been eligible for ASCT to have been included in the study (see Section 2.3.1). Despite this uncertainty, the results of the total population of the MAIA study were used in this benefit assessment (see Section 2.3.1 for the corresponding justification).

Patient randomization was stratified by the factors of International Staging System (ISS) stage (I versus II versus III), region (North America versus others), and age (< 75 years versus ≥ 75 years). A total of 737 patients were randomly allocated to the study arms, of which 368 were in the intervention arm receiving daratumumab + lenalidomide + dexamethasone and 369 in the control arm receiving lenalidomide + dexamethasone.

In both study arms, treatment was administered in 4-week cycles until disease progression, unacceptable toxicity, withdrawal of consent, or study end. The drugs were administered largely in accordance with the specifications in the SPC [20,21]. If any component of the treatment regimen was discontinued, continued treatment with the remaining components was allowed.

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

Data cut-off dates

The MAIA study started in March 2015 and had not yet been completed at the time this benefit assessment was written. A further analysis of overall survival is planned after 260 deaths. The final data cut-off is planned after 330 deaths or 7 years after the last patient was included. With the current dossier, the company presents results on the following data cut-off dates:

- Data cut-off on 24 September 2018: predefined interim analysis scheduled to occur after reaching 234 events concerning the primary outcome of PFS
- Data cut-off on 10 June 2019: data cut-off asked for by the EMA

The 2nd data cut-off represents the longest available follow-up period and is the primary one used in this benefit assessment, unless stated otherwise. Since this data cut-off was requested by the EMA, it can be assumed to be free of reporting bias.

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

Table 8: Planned follow-up observation periods– RCT, direct comparison: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone

Study **Outcome category** **Outcome**	**Planned follow-up**
MAIA	
Mortality	
Overall survival	Until study end, death, or withdrawal of consent (whichever is earlier)
Morbidity	
Symptoms / health status (EORTC-QLQ-C30 symptom scales / EQ-5D-VAS)	For 16 weeks after start of disease progression
Health-related quality of life	For 16 weeks after start of disease progression
Adverse events	
All outcomes of the adverse events category	Either for 30 days after the last administration of the study drug or until withdrawal of consent or until the start of subsequent anti-myeloma therapy (whichever is earlier)

AE: adverse event; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D VAS: European Quality of Life Questionnaire – 5 Dimensions Visual Analogue Scale; RCT: randomized controlled trial; SAE: serious adverse event

The follow-up observation periods for the outcomes of morbidity, health-related quality of life, and adverse events are systematically shortened. For instance, the outcomes from the adverse events category were collected only for the 30 days beyond the period patients were treated with the study drugs. The outcomes of health status and health-related quality of life were followed up beyond progression, but for a maximum of 16 weeks after the start of disease progression. However, to be able to draw a reliable conclusion for the entire study period or until patient death, these outcomes, like survival, would have to be surveyed and analysed over the entire study period.

Table 9 shows the patient characteristics for the included study.

Table 9: Characterization of the study population – RCT, direct comparison: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone (multi-page table)

Study Characteristics **Category**	**Daratumumab + lenalidomide + dexamethasone** **N[a] = 368**	**Lenalidomide + dexamethasone** **N[a] = 369**
MAIA		
Age [years], mean (SD)	74 (5)	74 (6)
< 65 years, n (%)	4 (1.1)	4 (1.1)
65 to < 70 years, n (%)	74 (20.1)	73 (19.8)
70 to < 75 years, n (%)	130 (35.3)	131 (35.5)
≥ 75 years, n (%)	160 (43.5)	161 (43.6)
Sex [f/m], %	49/51	47/53
Race/ethnicity, n (%)		
White	336 (91.3)	339 (91.9)
Black, African American	12 (3.3)	16 (4.3)
Other[b]	9 (2.4)	9 (2.4)
Unknown / not reported[c]	11 (3.0)	5 (1.4)
ECOG-PS, n (%)		
0	127 (34.5)	123 (33.3)
1	178 (48.4)	187 (50.7)
2	63 (17.1)	59 (16.0)
ISS[d], n (%)		
I	98 (26.6)	103 (27.9)
II	163 (44.3)	156 (42.3)
III	107 (29.1%)	110 (29.8)
Disease duration: Period from initial diagnosis to randomization [months], mean (SD)	1.4 (1.5)	1.3 (1.4)
Number of osteolytic lesions, n (%)		
None	100 (27.2)	93 (25.2)
1–3	103 (28.0)	97 (26.3)
4–10	88 (23.9)	90 (24.4)
> 10	77 (20.9)	89 (24.1)
Cytogenetic risk profile, n (%)[e]		
Standard risk	271 (85.0)	279 (86.4)
High risk	48 (15.0)	44 (13.6)
Treatment discontinuation, n (%)	143 (39.3)	233 (63.8)
Study discontinuation, n (%)	93 (25.3)	123 (33.3)

Table 9: Characterization of the study population – RCT, direct comparison: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone (multi-page table)

Study Characteristics Category	Daratumumab + lenalidomide + dexamethasone Na = 368	Lenalidomide + dexamethasone Na = 369

a. Number of randomized patients. Values which are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. IQWiG calculation; includes Asian, Hawaiian and Pacific Islander, and others.
c. IQWiG calculations.
d. ISS based on serum β2-microglobulin and albumin values.
e. Cytogenetic risk is based on FISH or karyotyping and refers to the following high-risk markers: del(17p), t(4;14) deletion and t(14;16) translocation; determined for only 319 patients in the intervention arm and 323 in the control arm.

ECOG-PS: Eastern Cooperative Oncology Group Performance Status; f: female; FISH: fluorescence in situ hybridization; ISS: International Staging System; IQWiG: Institute for Quality and Efficiency in Health Care; m: male; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation

Patient characteristics are balanced between the two treatment arms of the MAIA study. Patients were 74 years of age on average and predominantly white (approximately 92%). Women made up approximately 50% of patients in both study arms. The majority (83%) of included patients had an ECOG-PS of 0 or 1. About 30% of patients had tumours in ISS stage I, about 40% in stage II, and about 30% in stage III. A marked difference was found in the proportion of patients with treatment discontinuation (39.3% in the intervention arm versus 63.8% in the comparator arm). In both treatment arms, the most common reason for treatment discontinuation was disease progression.

Table 10 shows the mean and median patient treatment duration as well as the mean and median follow-up observation periods for individual outcomes.

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

Study **Duration of the study phase** Outcome category	**Daratumumab + lenalidomide + dexamethasone**	**Lenalidomide + dexamethasone**
MAIA		
Treatment duration [months][a]	N = 364	N = 365
Median [min; max]	32.4 [0.1; 49.0]	22.6 [0; 49.0]
Mean (SD)	28.5 (12.7)	21.7 (13.7)
Follow-up observation [months]	N = 368	N = 369
Overall survival		
Median [min; max]	36.7 (0; 49.0)	35.9 (0; 49.9)
Mean (SD)	32.1 (10.7)	30.2 (11.5)
Morbidity, health-related quality of life (EQ-5D/EORTC QLQ-C30)		
Median [min; max]	27.7 [N/A; N/A] / 28.2 [N/A; N/A]	21.5 [N/A; N/A] / 21.8 [N/A; N/A]
Mean (SD)	N/A / N/A	N/A / N/A
Adverse events		
Median [min; max]	32.7 [N/A; N/A]	23.5 [N/A; N/A]
Mean (SD)	N/A	N/A

a. Data on the treatment duration of the triple or dual combination; no information available on the treatment duration for the individual drug components.

EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; max: maximum; min: minimum; N: number of analysed patients; N/A: not available; RCT: randomized controlled trial; SD: standard deviation

The median treatment duration in the MAIA study is higher in the intervention arm than in the control arm (median: 32.4 versus 22.6). The median follow-up observation period for the outcome of overall survival is comparable for the study arms. Since the follow-up observation periods for the outcomes of the categories of morbidity, health-related quality of life, and adverse events are linked to treatment duration (see Table 8), the follow-up observation periods for these outcomes are also longer in the intervention arm than in the comparator arm.

Table 11 shows which follow-up therapies patients received after discontinuing the study drug.

Table 11: Information on antineoplastic follow-up therapies – RCT, direct comparison: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone (multi-page table)

Study **Drug class** **Drug**	**Patients with follow-up therapy n (%)**	
	Daratumumab + lenalidomide + dexamethasone **N = 364**	**Lenalidomide + dexamethasone** **N = 365**
MAIA		
1st follow-up therapy[a]		
Total	82 (22.5)	146 (40.0)
Bortezomib-cyclophosphamide-dexamethasone	13 (15.9)	29 (19.9)
Bortezomib-dexamethasone	15 (18.3)	25 (17.1)
Bortezomib-melphalan-prednisone	12 (14.6)	26 (17.8)
Lenalidomide-dexamethasone	8 (9.8)	13 (8.9)
Daratumumab-bortezomib-dexamethasone	1 (1.2)	7 (4.8)
Autologous stem cell transplantation	2 (2.4)	5 (3.4)
Bortezomib-lenalidomide-dexamethasone	4 (4.9)	3 (2.1)
Bortezomib-pomalidomide-dexamethasone	3 (3.7)	2 (1.4)
Carfilzomib-cyclophosphamide-dexamethasone	0 (0)	5 (3.4)
Carfilzomib-dexamethasone	2 (2.4)	3 (2.1)
Bortezomib-thalidomide-dexamethasone	2 (2.4)	1 (0.7)
Daratumumab monotherapy	1 (1.2)	2 (1.4)
Daratumumab-lenalidomide-dexamethasone	1 (1.2)	2 (1.4)
Pomalidomide-dexamethasone	1 (1.2)	2 (1.4)
Bendamustine-bortezomib-dexamethasone	0 (0)	2 (1.4)
Bortezomib-cyclophosphamide-melphalan	1 (1.2)	1 (0.7)
Bortezomib-cyclophosphamide-thalidomide	0 (0)	2 (1.4)
Cyclophosphamide-doxorubicin-vincristine	1 (1.2)	1 (0.7)
Daratumumab-bortezomib-melphalan-prednisone	0 (0)	2 (1.4)
Daratumumab-cyclophosphamide-dexamethasone	2 (2.4)	0 (0)
Daratumumab-pomalidomide-dexamethasone	0 (0)	2 (1.4)
Dexamethasone	0 (0)	2 (1.4)
Lenalidomide-cyclophosphamide-dexamethasone	2 (2.4)	0 (0)
Melphalan-prednisone	0 (0)	2 (1.4)
Pomalidomide-dexamethasone-ixazomib citrate	1 (1.2)	1 (0.7)
5-Fluorouracil-folinic acid-oxaliplatin	1 (1.2)	0 (0)
Bendamustine-rituximab	1 (1.2)	0 (0)
Bortezomib-cyclophosphamide-dexamethasone-carfilzomib	0 (0)	1 (0.7)
Bortezomib-cyclophosphamide-dexamethasone-daratumumab	0 (0)	1 (0.7)

Table 11: Information on antineoplastic follow-up therapies – RCT, direct comparison: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone (multi-page table)

Study **Drug class** **Drug**	**Patients with follow-up therapy n (%)**	
	Daratumumab + lenalidomide + dexamethasone **N = 364**	**Lenalidomide + dexamethasone** **N = 365**
Bortezomib-cyclophosphamide-dexamethasone-doxorubicin	1 (1.2)	0 (0)
Bortezomib-dexamethasone-doxorubicin	1 (1.2)	0 (0)
Bortezomib-dexamethasone-panobinostat	1 (1.2)	0 (0)
Cyclophosphamide-dexamethasone	0 (0)	1 (0.7)
Cyclophosphamide-dexamethasone-doxorubicin-vincristine	0 (0)	1 (0.7)
Cyclophosphamide-dexamethasone-ixazomib citrate	0 (0)	1 (0.7)
Ixazomib citrate	1 (1.2)	0 (0)
Ixazomib citrate-dexamethasone	1 (1.2)	0 (0)
Lenalidomide-cyclophosphamide-dexamethasone-ixazomib	1 (1.2)	0 (0)
Lenalidomide-dexamethasone-elotuzumab	1 (1.2)	0 (0)
Lenalidomide-ixazomib citrate	1 (1.2)	0 (0)
Thalidomide-prednisone	0 (0)	1 (0.7)

a. No information provided on further follow-up therapies.

n: number of patients with follow-up therapy; N: number of analysed patients; RCT: randomized controlled trial

In both study arms, starting follow-up anti-myeloma therapy was allowed only after confirmed disease progression. There were no restrictions regarding the type of follow-up therapy, and the choice of follow-up anti-myeloma therapy was at the discretion of the treating physician. At the data cut-off date of 10 June 2019, the proportion of patients with follow-up therapy was lower in the intervention arm than in the control arm (22.5% versus 40.0%). The types of follow-up therapy in the two study arms were sufficiently comparable.

Pursuant to the study protocol, patients in the comparator arm had the option of receiving follow-up daratumumab therapy in accordance with local approval. In the 1st follow-up therapy, 5 patients in the intervention arm (1.4%) and 16 patients in the comparator arm (4.3%) received daratumumab either as monotherapy or combination therapy. For 7 patients, follow-up therapy also included ASCT.

Risk of bias across outcomes (study level)

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

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

Study	Adequate generation of the randomization sequence	Allocation concealment	Blinding		Absence of reporting bias	No other aspects	Risk of bias at study level
			Patients	Providers			
MAIA	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

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

Restrictions resulting from the open-label study design are described in Section 2.4 under risk of bias at outcome level.

Transferability of the study results to the German healthcare context

The company reports that the vast majority of patients (73%) is from Europe and Australia, while 27% of patients are from North America, and that 91% of all patients are white. According to the company, there was no evidence of any biodynamic or kinetic differences which would meaningfully impact study results between the individual involved population groups or between individual countries and Germany. Hence, the company posits that the results are generally transferable to the German healthcare context, under consideration of the uncertainty associated with the transferability of clinical data.

The company does not present any further information on the transferability of study results to the German healthcare context.

2.4 Results on added benefit

2.4.1 Included outcomes

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

- Mortality
  - overall survival
- Morbidity
  - health status (as measured with the European Quality of Life Questionnaire – 5 Dimensions Visual Analogue Scale [EQ-5D VAS])
  - symptoms measured with the symptom scales of the European Organization and Treatment of Cancer Quality of Life Questionnaire Core30 (EORTC QLQ-C30)
- Health-related quality of life
  - health-related quality of life measured with the EORTC QLQ-C30 functional scales
- Adverse events
  - SAEs
  - discontinuation due to AEs
  - severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] ≥ grade 3)
  - infusion-related reaction
  - further specific AEs, if any

The choice 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 + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone

Study	Outcomes								
	Overall survival	**Health status (EQ-5D VAS)**	**Symptoms (EORTC QLQ-C30 symptom scales)**	**Health-related quality of life (EORTC QLQ-C30 – functional scales)**	**SAEs**	**Discontinuation due to AEs**	**Severe AEs (CTCAE grade ≥ 3)**	**Infusion-related reaction**	**Further specific AEs[d]**
MAIA	Yes	Yes[a]	Yes	Yes	Yes	No[b]	Yes	No[c]	Yes

a. The analyses on the response criteria of 7 or 10 points are not usable due to a lack of validity of these response criteria (see benefit assessment A18-33 [22]). Continuous analyses are available only for the 1st data cut-off date of 24/09/2018.

b. No usable data: The company presented only analyses on discontinuation of the entire treatment regimen due to AEs. These analyses are not meaningfully interpretable in the present situation, where the intervention arm involves 3 drugs and the comparator arm 2 drugs (see Section 2.4.3). No analyses are available on the discontinuation of one or more drug components due to AEs.

c. No usable data since the operationalization of the outcome is unsuitable for adequately representing an infusion-related reaction (see Section 2.4.3).

d. The following events are considered (MedDRA coding): "chills (PT, AEs)", "respiratory, thoracic, and mediastinal disorders (SOC, AEs)", "infections and infestations (SOC, SAEs)", "skin and subcutaneous tissue disorders (SOC, CTCAE grade ≥ 3)", "neutropenia (PT CTCAE grade≥ 3)", "anaemia (PT, CTCAE grade ≥ 3)."

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D VAS: European Quality of Life Questionnaire – 5 Dimensions Visual Analogue Scale; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: system organ class

2.4.2 Risk of bias

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

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

Study	Study level	Outcomes								
		Overall survival	Health status (EQ-5D VAS)	Symptoms (EORTC QLQ-C30 symptom scales)	Health-related quality of life (EORTC QLQ-C30 – functional scales)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Infusion-related reaction	Other specific AEs[f]
MAIA	L	L	H[a]	H[a, b]	H[a, b]	H[b]	-[c]	L	-[d]	H[e]

a. Lack of blinding, in some cases in connection with subjective recording of outcomes.
b. Incomplete observations for potentially informative reasons.
c. No usable data. The company presented analyses of discontinuation due to AEs only for discontinuation of the entire treatment regimen. These analyses are not meaningfully interpretable in the present situation, where the intervention arm involves 3 drugs and the comparator arm 2 drugs. Lack of analyses calculating the hazard ratio for discontinuation of at least one drug component due to AEs (see Section 2.4.3).
d. No usable data since the operationalization of the outcome is unsuitable for adequately representing an infusion-related reaction (see Section 2.4.3).
e. Lack of blinding, in some cases with subjective recording of outcomes, for selected specific AEs as well as incomplete observations for potentially informative reasons.
f. The following events are considered (MedDRA coding): "chills (PT, AEs)", "respiratory, thoracic, and mediastinal disorders (SOC, AEs)", "infections and infestations (SOC, SAEs)", "skin and subcutaneous tissue disorders (SOC, CTCAE grade ≥ 3)", "neutropenia (PT CTCAE grade≥ 3)", "anaemia (PT, CTCAE grade ≥ 3)."

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D VAS: European Quality of Life Questionnaire – 5 Dimensions Visual Analogue Scale; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: system organ class

The risk of bias for the results on the outcome of overall survival is rated as low. This concurs with the company's assessment.

For each of the outcomes on symptoms (symptom scales of the EORTC QLQ-C30), health-related quality of life (functional scales of the EORTC QLQ-C30), and health status (EQ-5D VAS), the risk of bias of results is rated as high due to lack of blinding in connection with subjective recording of outcomes. For the outcomes on symptoms and health-related quality of life, another reason for this rating is the fact that the planned repeated measurements over time are incomplete for a considerable percentage of patients; this was due to potentially informative reasons, such as treatment discontinuation due to progression. The company mentions this as another reason for a high risk of bias for the latter outcomes as well.

For the outcome of severe AEs (CTCAE grade ≥ 3), the risk of bias of results is rated as low: Firstly, events occurred in a large percentage of patients (approximately 92% of patients in the intervention arm and approximately 86% of patients in the control arm), and in the majority of these patients, they took place soon after randomization. Secondly, censoring did not occur to a relevant extent in the first months, during which the Kaplan-Meier curves already diverged (Table 17). Therefore, an increased risk of bias due to potentially informative censoring does not exist for the estimated hazard ratio. This assessment of the risk of bias concurs with the company's assessment.

The company rates the outcomes of SAEs as well as severe AEs (CTCAE grade ≥ 3) as having a low risk of bias. In comparison with severe AEs (CTCAE grade ≥ 3), SAEs occurred later and much less commonly; therefore, incomplete observation for potentially informative reasons was possible for the entire course of the study in a considerable percentage of patients; as a result, there is a high risk of bias for this outcome.

The results of the specific AEs used in the MAIA study, namely chills (PT, AEs), respiratory, thoracic, and mediastinal disorders (SOC, AEs), infections and infestations (SOC, SAEs), skin and subcutaneous tissue disorders (SOC, CTCAE grade ≥ 3), neutropenia (PT CTCAE grade ≥ 3), and anaemia (PT, CTCAE grade ≥ 3), are deemed to have a high risk of bias, likewise due to incomplete observations for potentially informative reasons. For the specific AEs of chills (PT, AEs) and respiratory, thoracic, and mediastinal disorders (SOC, AEs), a further reason for this rating is lack of blinding. This assessment of the risk of bias was done after the fact; the company did not provide an assessment.

2.4.3 Results

Table 15 and Table 16 summarize the results on the comparison of daratumumab in combination with lenalidomide and dexamethasone versus lenalidomide and dexamethasone for adult patients with newly diagnosed multiple myeloma who are ineligible for ASCT.

Where necessary, the data from the company's dossier are complemented by IQWiG calculations.

Table 15: Results (mortality, morbidity, quality of life, adverse events) – RCT, direct comparison: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone (multi-page table)

Study **Outcome category** **Outcome**	**Daratumumab + lenalidomide + dexamethasone**		**Lenalidomide + dexamethasone**		**Daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone**
	N	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p value[a]**
MAIA (data cut-off 10/06/2019)					
Mortality					
Overall survival	368	NR 85 (23.1)	369	NR [47.3; NR] 103 (27.9)	0.78 [0.58; 1.04]; 0.089
Morbidity					
EORTC QLQ-C30 – symptom scales[b]					
Fatigue	368	4.9 [4.7; 7.5] 226 (61.4%)	369	4.8 [4.6; 7.5] 218 (59.1)	0.86 [0.71; 1.04]; 0.127
Nausea and vomiting	368	38.0 [26.7; NR] 148 (40.2)	369	30.1 [21.3; NR] 140 (37.9)	0.92 [0.73; 1.16]; 0.464
Pain	368	35.0 [27.2; NR] 147 (39.9)	369	18.0 [10.8; 27.3] 162 (43.9)	0.68 [0.54; 0.85]; < 0.001
Dyspnoea	368	27.2 [21.2; 36.2] 168 (45.7)	369	15.7 [10.3; 22.0] 170 (46.1)	0.79 [0.64; 0.99]; 0.036
Insomnia	368	16.9 [10.2; 28.5] 184 (50.0)	369	16.5 [10.2; 27.8] 166 (45.0)	0.94 [0.76; 1.16]; 0.550
Appetite loss	368	34.4 [27.7; NC] 149 (40.5)	369	26.0 [11.5; 32.2] 155 (42.0)	0.80 [0.64; 1.01]; 0.059
Constipation	368	21.7 [10.5; 32.5] 174 (47.3)	369	16.1 [7.7; 26.0] 167 (45.3)	0.86 [0.70; 1.07]; 0.181
Diarrhoea	368	15.7 [10.3; 16.3] 227 (61.7)	369	10.6 [10.0; 16.0] 196 (53.1)	0.98 [0.81; 1.19]; 0.845
Health-related quality of life					
EORTC QLQ-C30 – functional scales[b]					
Global health status	368	26.7 [17.5; NC] 167 (45.4)	369	21.3 [11.4; 27.7] 160 (43.4)	0.87 [0.70; 1.08]; 0.201
Physical functioning	368	NR [27.8; NC] 147 (39.9)	369	21.5 [12.7; 33.5] 158 (42.8)	0.76 [0.61; 0.96]; 0.018
Role functioning	368	10.2 [7.3; 18.2] 197 (53.5)	369	10.2 [6.8; 15.7] 189 (51.2)	0.90 [0.74; 1.10]; 0.301
Emotional functioning	368	NR [32.5; NC] 140 (38.0)	369	28.6 [16.5; 40.5] 138 (37.4)	0.84 [0.66; 1.06]; 0.140
Cognitive functioning	368	8.0 [7.4; 15.7] 221 (60.1)	369	10.2 [7.5; 11.6] 193 (52.3)	0.96 [0.79; 1.17]; 0.689
Social functioning	368	10.7 [7.5; 21.2] 196 (53.3)	369	7.5 [4.8; 10.4] 197 (53.4)	0.81 [0.66; 0.99]; 0.038

Table 15: Results (mortality, morbidity, quality of life, adverse events) – RCT, direct comparison: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone (multi-page table)

Study **Outcome category** **Outcome**	**Daratumumab + lenalidomide + dexamethasone**		**Lenalidomide + dexamethasone**		**Daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone**
	N	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p value[a]**
Adverse events					
AEs (supplementary information)	364	0.03 [NC; NC] 364 (100)	365	0.2 [0.1; 0.3] 362 (99.2)	–
SAEs	364	12.9 [7.6; 16.9] 248 (68.1)	365	9.8 [7.6; 12.7] 247 (67.7)	0.92 [0.77; 1.10]; 0.334
Severe AEs (CTCAE grade ≥ 3)	364	0.7 [0.7; 1.1] 336 (92.3)	365	1.9 [1.6; 2.9] 315 (86.3)	1.35 [1.15; 1.58]; < 0.001
Discontinuation due to AEs	No usable data[c]				
Specific AEs					
Infusion-related reaction	No usable data[d]				
Chills (PT, AEs)		NR 47 (12.9)		NR 6 (1.6)	7.87 [3.36; 18.41]; < 0.001
Respiratory, thoracic, and mediastinal disorders (SOC, AEs)		4.7 [2.8; 7.4] 248 (68.1)		19.4 [12.7; 31.3] 172 (47.1)	1.78 [1.46; 2.17]; < 0.001
Infections and infestations (SOC, SAEs)		NR [45.0; NC] 130 (35.7)		NR 90 (24.7)	1.32 [1.01; 1.74]; 0.042
Skin and subcutaneous tissue disorders (SOC, CTCAE grade ≥ 3)		NR 17 (4.7)		NR 33 (9.0)	0.47 [0.26; 0.85]; 0.012
Neutropenia (PT, CTCAE grade ≥ 3)		23.8 [12.9; NC] 186 (51.1)		NR 129 (35.3)	1.63 [1.30; 2.04]; < 0.001
Anaemia (PT, CTCAE grade ≥ 3)		NR 49 (13.5)		NR 75 (20.5)	0.54 [0.38; 0.78]; 0.001

a. HR, CI, and p-value: Cox proportional hazards model stratified by the factors of ISS stage, region, and age.
b. Time to deterioration; defined as a score increase by ≥ 10 points (for symptom scales) or score decrease by ≥ 10 points (for functional scales) compared to baseline.
c. The company presented analyses on discontinuation due to AEs only for discontinuation of the entire treatment regimen. These analyses are not meaningfully interpretable in the present situation, where the intervention arm involves 3 drugs and the comparator arm 2 drugs. There is a lack of analyses calculating the hazard ratio for discontinuation of at least one drug component due to AEs (see below).
d. No usable data since the operationalization of the outcome is unsuitable for adequately representing an infusion-related reaction (see below).

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; HR: hazard ratio; ISS: International Staging System; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; NR: not reached; RCT: randomized controlled trial; SAE: serious adverse event

Table 16: Results (morbidity) – RCT, direct comparison: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone

Study Outcome category Outcome	Daratumumab + lenalidomide + dexamethasone			Lenalidomide + dexamethasone			Daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone
	N[a]	Values at study start Mean (SD)	Change by cycle 12 Mean[b] [95% CI]	N[a]	Values at study start Mean (SD)	Change by cycle 12 Mean[b] [95% CI]	MD[b] [95% CI]; p value
MAIA (data cut-off 24/09/2018)[c]							
Morbidity							
Health status							
EQ-5D VAS[d]	349	62.6 (22.3)	10.1 [8.1; 12.1]	346	62.7 (21.5)	4.9 [2.8; 7]	5.2 [2.4; 8]; < 0.001 Hedges' g[e]: 0.28 [0.13; 0.43]

a. Number of patients considered in the analysis for the calculation of the effect estimation; baseline values may be based on other patient numbers.
b. Mixed-effect model repeat measurement (MMRM), stratified by ISS stage, region, and age. Effect represents the difference of changes (compared to baseline) between the treatment groups at Cycle 12.
c. No continuous analyses available for data cut-off 10/06/2019.
d. Higher (increasing) values indicate better health status; positive effects (intervention minus control) indicate an advantage for the intervention.
e. IQWiG calculations.

CI: confidence interval; EQ-5D VAS: European Quality of Life Questionnaire – 5 Dimensions Visual Analogue Scale; MD: mean difference; MMRM: mixed effect model repeated measurement; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation

Based on the available data, at most hints, e.g. of an added benefit, can be determined for all outcomes (for reasons, see Section 2.3.1).

Mortality

Overall survival

For the outcome of overall survival, no statistically significant difference between treatment groups was found. Consequently, there is no hint of added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

Health status (EQ-5D VAS)

For the outcome of health status as measured by EQ-5D VAS, mean value comparisons show a statistically significant difference between treatment arms for the available data cut-off date of 24 September 2018. To check the relevance of the result, the SMD was considered in the

form of Hedges' g. The 95% confidence interval of the SMD in the form of Hedges' g is not fully outside of the irrelevance range of -0.2 to 0.2. Hence, the effect cannot be rated as relevant. Consequently, there is no hint of added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone; an added benefit is therefore not proven.

This assessment of added benefit concurs with the company's assessment insofar as the company does not derive any added benefit either, but it reached this conclusion on the basis of responder analyses. The analyses of the EQ-5D on the basis of responder analyses are presented as supplementary information in Appendix C of the full dossier assessment.

Symptoms (EORTC QLQ-C30 – symptom scales)

Symptom outcomes were recorded using the symptom scales of the EORTC QLQ-C30. In each case, time to deterioration by ≥ 10 points was the criterion.

For the pain scale, a statistically significant difference was found in favour of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone. Consequently, there is a hint of added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone.

For the dyspnoea scale, a statistically significant difference was found in favour of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone. The difference, however, is no more than marginal for this outcome in the category of non-serious/non-severe symptoms/late complications. This does not result in a hint of added benefit; an added benefit is therefore not proven for this outcome.

For each of the outcomes of fatigue, nausea and vomiting, insomnia, appetite loss, constipation, and diarrhoea, no statistically significant difference between treatment arms was found. For each of these outcomes, there is consequently no hint of added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone; an added benefit is therefore not proven for these outcomes. This concurs with the company's assessment.

The assessment on the morbidity outcomes deviates from that of the company, which derived an indication of added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone for the morbidity outcomes on the basis of the pain and dyspnoea scales as well as time to subsequent anti-myeloma therapy and disease progression.

Health-related quality of life

Outcomes for health-related quality of life were collected using the functional scales of the EORTC QLQ-C30. In each case, time to deterioration by ≥ 10 points was the criterion.

For each of the outcomes of physical functioning and social functioning, a statistically significant difference was found in favour of daratumumab + lenalidomide + dexamethasone

in comparison with lenalidomide + dexamethasone. Consequently, for each of these two outcomes, there is a hint of added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone.

For each of the outcomes of global health status, role functioning, emotional functioning, and cognitive functioning, no statistically significant difference between treatment arms was found. For each of these outcomes, there is consequently no hint of added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone; an added benefit is therefore not proven for these outcomes.

This assessment deviates from that of the company, which derives an indication of added benefit for the entire outcome category of health-related quality of life on the basis of the scales of physical functioning and social functioning.

Adverse events

SAEs

For the outcome of SAEs, no statistically significant difference between treatment arms was found. Consequently, for SAEs, there is no hint of greater or lesser harm of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone; greater or lesser harm is therefore not proven.

Severe AEs (CTCAE ≥ grade 3)

For the outcome of severe AEs (CTCAE grade ≥ 3), a statistically significant difference to the disadvantage of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone was found. Consequently, there is a hint of greater harm of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone.

Discontinuation due to AEs

For the outcome of discontinuation due to AEs, no usable data were available. The company presented analyses of discontinuation due to AEs only for discontinuation of the entire treatment regimen. Accordingly, 30 patients (8.2%) in the intervention arm and 63 patients (17.3%) in the comparator arm had an AE which lead to discontinuation of the entire treatment regimen. No analyses calculating the hazard ratio for discontinuation of at least one drug component due to AEs were available. The study report does at least contain data on the discontinuation of any component for an earlier data cut-off date (24 September 2018). Accordingly, unlike discontinuation of the entire treatment regimen, discontinuations of any component are more common in the intervention arm than in the control arm (114 [31.3%] versus 97 [26.6%]).

The MAIA study compared a 3-drug combination in the intervention arm with a 2-drug combination in the comparator arm. The study protocol allowed patients who discontinued a single component of the respective treatment regimen to continue treatment with the remaining

components. For the comparator arm, however, continuing treatment with dexamethasone monotherapy after discontinuation of lenalidomide is not an option and would be insufficient. This is reflected by the data on the proportions of patients with treatment discontinuation of individual components; these data are only available for the data cut-off date of 24 September 2018. It shows that, in the comparator arm, discontinuation of lenalidomide almost always involved discontinuation of the entire treatment regimen: 62 patients (17.0%) with discontinuation due to lenalidomide versus 58 patients (15.9%) with discontinuation of the complete treatment regimen. In the intervention arm, in contrast, 76 patients (20.9%) discontinued lenalidomide, but only 26 patients (7.2%) discontinued the entire treatment regimen. Consequently, an analysis on discontinuation of the entire treatment regimen cannot be meaningfully interpreted in the present situation, where the discontinuation of one component goes hand in hand with the discontinuation of the entire treatment regimen in the comparator arm, but not in the intervention arm. Irrespective of the above, discontinuation of at least one drug component is preferable as an outcome since every AE which leads to discontinuation of any treatment component is relevant.

Infusion-related reaction

No usable data are available for the outcome of infusion-related reaction. The MAIA study documented infusion-related reactions in the case report form. However, infusions were administered only in the intervention arm, while patients in the control arm did not receive a placebo infusion. Infusion-related reactions can therefore be recorded only in the intervention arm; therefore, the study arms cannot be compared in this respect. Moreover, in this situation, any event which occurred in the intervention arm is assumed to be due to the drug, and the difference between study arms would likely be smaller if a placebo infusion were used in the comparator arm. Due to the open-label study design, no usable data are therefore available on this outcome for the benefit assessment.

Further specific AEs

Skin and subcutaneous tissue disorders (SOC, CTCAE grade ≥ 3), anaemia (PT, CTCAE grade ≥ 3)

For each of the outcomes of skin and subcutaneous tissue disorders (SOC, CTCAE grade ≥ 3) and anaemia (PT, CTCAE grade ≥ 3), a statistically significant difference was found in favour of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone. Consequently, Consequently, these 2 specific AEs provide a hint of lesser harm of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone. However, it is questionable whether the effect on the outcome of anaemia (PT, CTCAE grade ≥ 3) is actually attributable to the outcome category of adverse events or whether it rather reflects the clinical picture of the underlying disease.

Chills (PT, AEs), respiratory, thoracic, and mediastinal disorders (SOC, AEs), infections and infestations (SOC, SAEs), and neutropenia (PT CTCAE grade≥ 3)

For each of the outcomes of chills (PT, AEs), respiratory, thoracic, and mediastinal disorders (SOC, AEs), infections and infestations (SOC, SAEs), and neutropenia (PT, CTCAE grade ≥ 3), a statistically significant difference was found to the disadvantage of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone. Consequently, for these 4 specific AEs, there is a hint of greater harm of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone.

The assessments of harm outcomes deviate from those of the company, which derived an indication of minor added benefit for the entire outcome category of adverse events, primarily on the basis of discontinuation due to AEs.

2.4.4 Subgroups and other effect modifiers

For the MAIA study, no subgroup analyses were used in the benefit assessment. This is justified as follows:

The MAIA study is relevant for the present research question. However, the results for the included population (patients ineligible for ASCT) are subject to uncertainty (see Section 2.3.1). Any subsequent subgroup analyses are therefore subject to additional uncertainty: It would be unknown how patients eligible for ASCT are distributed among the potential subgroups and to what extent subgroup results would be biased as a result. The results from any subgroup analyses are therefore assessed as not interpretable.

2.5 Probability and extent of added benefit

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

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

2.5.1 Assessment of added benefit at outcome level

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

Determination of the outcome category for outcomes on symptoms and adverse events

The dossier does not permit an inference for all outcomes considered in the present benefit assessment whether they were non-serious/non-severe or serious/severe, or this benefit assessment deviated from the assessment provided in the dossier. The classification of these outcomes is justified below.

Pain and dyspnoea

The pain and dyspnoea symptom scales of the EORTC QLQ-C30 questionnaire are considered "non-serious/non-severe" because the company's dossier does not permit an inferences as to whether the patients' symptoms were in a range which is to be rated as serious/severe.

The severity rating for the symptom of dyspnoea concurs with that of the company. The symptom of pain, in contrast, is rated as a severe/serious symptom by the company. The company justifies its rating by a threshold of 66 points, which reportedly corresponds to severe pain according to Johnsen 2009 [23]. The pain scale of the EORTC QLQ-C30 consists of 2 items, which are each answered on a 4-point Likert scale (not at all, a little, quite a bit, very much). In Johnson 2009, the threshold of 66 points is mentioned because according to the scoring manual, at a score of at least 66 points on a symptom scale, the mean of all items entered in the scale (2 items for pain) is at least 3 (quite a bit). According to the company, 39.4% of patients had a pain scale score ≥ 66 points at the start of the study. Further, the company reports that 11.1% of patients with a pain score < 66 received opioids for pain management. For these patients, the company assumes that the opioid-based pain management leads to a lower pain score. Overall, the company concludes that 50.5% of patients suffered from serious/severe pain, and it therefore rated the symptom of pain as a serious/severe symptom.

The employed threshold of 66 points is based on the assumption that patients who, on average, report at least quite a bit of pain do suffer from serious/severe pain. However, rating any symptom as serious or severe requires information on adequately technically justified thresholds. This is not the case for the pain symptom scale.

Specific AEs

The outcomes of chills (PT, AEs) and respiratory, thoracic, and mediastinal disorders (SOC, AEs) are predominantly composed of non-serious/non-severe events; overall, these outcomes are therefore allocated to the category of non-serious/non-severe adverse events.

The company did not rate the severity of the outcome of respiratory, thoracic, and mediastinal disorders (SOC, AEs). Nor did the company use the outcome of chills (PT, AEs) to derive an added benefit.

Table 17: Extent of added benefit at outcome level: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone (multi-page table)

Outcome category **Outcome**	**Daratumumab + lenalidomide + dexamethasone vs.** **Lenalidomide + dexamethasone** **Median time to event (months) or change from baseline until Cycle 12** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
Overall survival	Median: NA vs. NA HR: 0.78 [0.58; 1.04]; p = 0.089	Lesser/added benefit not proven
Morbidity		
Health status		
EQ-5D VAS (data cut-off 24/09/2018)	Change: 10.1 vs. 4.9 points MD: 5.2 [2.4; 8]; p < 0.001 Hedges' g[c]: 0.28 [0.13; 0.43]	Lesser/added benefit not proven
Symptoms (EORTC QLQ-C30 symptom scales – deterioration by ≥ 10 points)		
Fatigue	Median: 4.9 vs. 4.8 HR: 0.86 [0.71; 1.04]; p = 0.127	Lesser/added benefit not proven
Nausea and vomiting	Median: 38.0 vs. 30.1 HR: 0.92 [0.73; 1.16]; p = 0.464	Lesser/added benefit not proven
Pain	Median: 35.0 vs. 18.0 HR: 0.68 [0.54; 0.85]; p < 0.001 Probability: Hint	Outcome category: non-serious/non-severe symptoms / late complications $0.80 \leq CI_u < 0.90$ Added benefit, extent: minor
Dyspnoea	Median: 27.2 vs. 15.7 HR: 0.79 [0.64; 0.99]; p = 0.036	Outcome category: non-serious/non-severe symptoms / late complications $0.90 \leq CI_u < 1.00$ Lesser benefit / added benefit not proven[d]
Insomnia	Median: 16.9 vs. 16.5 HR: 0.94 [0.76; 1.16]; p = 0.550	Lesser/added benefit not proven
Appetite loss	Median: 34.4 vs. 26.0 HR: 0.80 [0.64; 1.01]; p = 0.059	Lesser/added benefit not proven
Constipation	Median: 21.7 vs. 16.1 HR: 0.86 [0.70; 1.07]; p = 0.181	Lesser/added benefit not proven
Diarrhoea	Median: 15.7 vs. 10.6 HR: 0.98 [0.81; 1.19]; p = 0.845	Lesser/added benefit not proven

Table 17: Extent of added benefit at outcome level: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone (multi-page table)

Outcome category **Outcome**	**Daratumumab + lenalidomide + dexamethasone vs.** **Lenalidomide + dexamethasone** **Median time to event (months) or change from baseline until Cycle 12** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Health-related quality of life		
EORTC QLQ-C30 – functioning scales (deterioration by ≥ 10 points)		
Global health status	Median: 26.7 vs. 21.3 HR: 0.87 [0.70; 1.08]; p = 0.201	Lesser benefit / added benefit not proven
Physical functioning	Median: NR vs. 21.5 HR: 0.76 [0.61; 0.96]; p = 0.018 Probability: Hint	Outcome category: health-related quality of life $0.90 \leq CI_o < 1.00$ Added benefit, extent: minor
Role functioning	Median: 10.2 vs. 10.2 HR: 0.90 [0.74; 1.10]; p = 0.301	Lesser/added benefit not proven
Emotional functioning	Median: NR vs. 28.6 HR: 0.84 [0.66; 1.06]; p = 0.140	Lesser/added benefit not proven
Cognitive functioning	Median: 8.0 vs. 10.2 HR: 0.96 [0.79; 1.17]; p = 0.689	Lesser/added benefit not proven
Social functioning	Median: 10.7 vs. 7.5 HR: 0.81 [0.66; 0.99]; p = 0.038 Probability: Hint	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Added benefit, extent: minor
Adverse events		
SAEs	Median: 12.9 vs. 9.8 HR: 0.92 [0.77; 1.10]; p = 0.334	Greater/lesser harm not proven
Severe AEs (CTCAE grade ≥ 3)	Median: 0.7 vs. 1.9 HR: 1.35 [1.15; 1.58]; p < 0.001 HR: 0.74 [0.63; 0.87][e] Probability: Hint	Outcome category: serious/severe adverse events $0.75 \leq CI_u < 0.90$ Greater harm; extent: considerable
Discontinuation due to AEs	No usable data[f]	Greater/lesser harm not proven
Infusion-related reaction	No usable data[g]	Greater/lesser harm not proven
Chills (PT, AEs)	Median: NR vs. NR HR: 7.87 [3.36; 18.41]; p < 0.001 HR: 0.13 [0.05; 0.30][e] Probability: Hint	Outcome category: non-serious/non-severe adverse events $CI_u < 0.80$ Greater harm; extent: considerable
Respiratory, thoracic, and mediastinal disorders (SOC, AEs)	Median: 4.7 vs. 19.4 HR: 1.78 [1.46; 2.17]; p < 0.001 HR: 0.56 [0.46; 0.68][e] Probability: Hint	Outcome category: non-serious/non-severe adverse events $CI_u < 0.80$ Greater harm; extent: considerable

Table 17: Extent of added benefit at outcome level: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone (multi-page table)

Outcome category **Outcome**	**Daratumumab + lenalidomide + dexamethasone vs.** **Lenalidomide + dexamethasone** **Median time to event (months) or change from baseline until Cycle 12** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Infections and infestations (SOC, SAEs)	Median: NR vs. NR HR: 1.32 [1.01; 1.74]; p = 0.042 HR: 0.76 [0.57; 0.99][e] Probability: Hint	Outcome category: serious/severe adverse events $0.90 \leq CI_u < 1.00$ Greater harm; extent: minor
Skin and subcutaneous tissue disorders (SOC, severe AEs CTCAE grade ≥ 3)	Median: NR vs. NR HR: 0.47 [0.26; 0.85]; p = 0.012 Probability: Hint	Outcome category: serious/severe adverse events $0.75 \leq CI_u < 0.90$ Lesser harm; extent: considerable
Neutropenia (PT, severe AEs CTCAE grade ≥ 3)	Median: 23.8 vs. NR HR: 1.63 [1.30; 2.04]; p < 0.001 HR: 0.61 [0.49; 0.77][e] Probability: Hint	Outcome category: serious/severe adverse events $0.75 \leq CI_u < 0.90$ Greater harm; extent: considerable
Anaemia (PT, severe AEs CTCAE grade ≥ 3)[h]	Median: NR vs. NR HR: 0.54 [0.38; 0.78]; p = 0.001 Probability: Hint	Outcome category: serious/severe adverse events $0.75 \leq CI_u < 0.90$ Lesser harm; extent: considerable

a. Probability given if a statistically significant and relevant effect is present.
b. Estimations on effect size are made depending on the outcome category with different limits based on the upper confidence limit (CI_u).
c. If the CI of Hedges' g is fully outside the irrelevance range [−0,2; 0,2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be derived.
d. The extent of the effect is no more than marginal for this non-serious/non-severe outcome.
e. IQWiG calculations, reversed direction of effect to enable use of limits to derive the extent of added benefit.
f. The company presented only analyses on discontinuation of the entire treatment regimen due to AEs. These analyses are not meaningfully interpretable in the present situation, where the intervention arm involves 3 drugs and the comparator arm 2 drugs (see Section 2.4.3). No analyses calculating the hazard ratio for discontinuation of at least one drug component due to AEs were available.
g. No usable data; this is because the operationalization of the outcome is unsuitable for adequately representing an infusion-related reaction (see Section 2.4.3).
h. It is questionable whether the effect is actually attributable to the outcome category of adverse events or rather reflects the clinical picture of the underlying disease.

AE: adverse event; CI: confidence interval; CI_u: upper confidence limit; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D VAS: European Quality of Life Questionnaire – 5 Dimensions Visual Analogue Scale; MD: mean difference; NR: not reached; SAE: serious adverse event

2.5.2 Overall conclusion on added benefit

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

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

Positive effects	**Negative effects**
Non-serious/non-severe symptoms / late complications ▪ Pain: Hint of added benefit – extent: minor	–
Health-related quality of life ▪ Physical functioning, social functioning: Hint of added benefit – extent: minor	–
Serious/severe AEs ▪ Specific AEs: Hint of lesser harm – extent: considerable (skin and subcutaneous tissue disorders, anaemia[a] [each severe AEs CTCAE grade ≥ 3])	Non-serious/non-severe AEs ▪ Specific AEs: Hint of greater harm – extent: considerable (including chills as well as respiratory, thoracic, and mediastinal disorders) Serious/severe AEs ▪ Severe AEs (CTCAE grade ≥ 3): Hint of greater harm – extent: considerable ▪ Specific AEs: Hint of greater harm; extent: minor to considerable (including neutropenia [severe AEs CTCAE grade ≥ 3] – extent: considerable; infections and infestations [SAE] – extent: minor)
a. It is questionable whether the effect is actually attributable to the outcome category of AEs or rather reflects the clinical picture of the underlying disease. AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; SAE: serious adverse event	

All things considered, both positive and negative effects of different extents were found for daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone. The negative effects concern exclusively AE outcomes (4 specific AEs , most with effects of considerable extent, and the total rate of severe AEs [CTCAE grade ≥ 3], with effects of considerable extent). Positive effects were of considerable extent for 2 specific AEs and of minor extent for pain as a symptom and for 2 of 6 scales on health-related quality of life. Taken all together, positive and negative effects are deemed balanced.

In summary, there is no proof of added benefit of daratumumab in combination with lenalidomide and dexamethasone in comparison with lenalidomide and dexamethasone for adult patients with newly diagnosed multiple myeloma who are ineligible for ASCT.

The result of the assessment of the added benefit of daratumumab in combination with lenalidomide and dexamethasone in comparison with the ACT is summarized in Table 19.

Table 19: Daratumumab – probability and extent of added benefit

Indication	**ACT[a]**	**Probability and extent of added benefit**
Daratumumab in combination with lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for stem cell transplantation	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 **Lenalidomide in combination with dexamethasone**	Added benefit not proven
a. Presentation of the respective 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 by the company is printed in **bold**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The assessment described above deviates from that of the company, which derived an indication of considerable added benefit.

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

References for English extract

Please see full dossier assessment for full reference list.

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

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The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a20-14-daratumumab-multiple-myeloma-benefit-assessment-according-to-35a-social-code-book-v.12975.html.