IQWiG Reports – Commission No. A21-126

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

Benefit assessment according to §35a Social Code Book V[1] (new scientific findings)

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 (neue wissenschaftliche Erkenntnisse)* (Version 1.1; Status: 16 February 2022). 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.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Daratumumab (newly diagnosed multiple myeloma, stem cell transplant unsuitable) – Benefit assessment according to §35a Social Code Book V

Commissioning agency
Federal Joint Committee

Commission awarded on
1 October 2021

Internal Commission No.
A21-126

Address of publisher
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

- Ingo Schmidt-Wolf

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 von Lier.

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

IQWiG employees involved in the dossier assessment

- Philip Kranz
- Florina Kerekes
- Stefan Kobza
- Ulrike Lampert
- Mattea Patt
- Daniela Preukschat
- Min Ripoll
- Cornelia Rüdig

Keywords: Daratumumab, Lenalidomide, Dexamethasone, Multiple Myeloma, Benefit Assessment, NCT02252172

Table of contents

List of tables[2]

Page

[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	EuroQoL 5 Dimensions Questionnaire
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
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)
SOC	System Organ Class
SPC	Summary of Product Characteristics
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (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 is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 1 October 2021. The company had already submitted a dossier for a previous benefit assessment of the drug to be assessed. The dossier was sent to IQWiG on 17 February 2020. On 6 July 2021, the company requested a reassessment of benefit because of new scientific findings. The reassessment refers to the MAIA study's 3rd data cut-off, which offers new insights on the outcome of all-cause survival.

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 research question presented in Table 2 resulted from the ACT specified by the Federal Joint Committee (G-BA).

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

Therapeutic indication	**ACT**[a]
Adult patients with newly diagnosed multiple myeloma who are ineligible for autologous 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. Presented is 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 of the company is printed in bold. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA's specification on the ACT. From the options listed 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.

Study pool and study design

MAIA study

The study pool for the benefit assessment consists 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 ongoing. It included patients (≥ 18 years of age) with newly diagnosed multiple myeloma who are 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 either 65 years of age or older or if they were under 65 years and had important 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. This uncertainty did not lead to the exclusion of the study but was taken into account in the assessment of the certainty of conclusions.

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

In both study arms, treatment was administered in 4-week cycles until disease progression, unacceptable toxicity, consent withdrawal, or study end. The drugs were used largely in accordance with the specifications of the Summary of Product Characteristics (SPC). 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 additional scientific evidence having become available, the most current data cut-off of 19 February 2021 was used for the present benefit assessment.

Risk of bias and assessment of the certainty of conclusions

The risk of bias across outcomes for the results of the MAIA study was rated as low. At the outcome level, the results are rated as highly biased for every outcome except overall survival and severe AEs (operationalized as Common Terminology Criteria for Adverse Event [CTCAE] grade ≥ 3). In addition, the certainty of conclusions is reduced because the percentage of MAIA participants eligible for ASCT is unclear. Hence, overall, at most hints, e.g. of an added benefit, can be derived.

Results

Mortality

Overall survival

For the outcome of all-cause survival, a statistically significant difference was found in favour of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone. This results in a hint of added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone.

Morbidity

Health status (EuroQoL 5 Dimensions Questionnaire visual analogue scale [EQ-5D VAS])

For the outcome of health status, operationalized as time to EQ-5D VAS deterioration by ≥ 15 points (scale range 0 to 100), 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 for this outcome.

Symptoms (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; [EORTC QLQ-C30])

Symptom outcomes were recorded using the EORTC QLQ-C30 scales. In each case, time to deterioration by ≥ 10 points (scale range 0 to 100) was analysed.

For the outcome of pain, a statistically significant difference was found in favour of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone. This results in a hint of added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone.

For the outcome of dyspnoea, a statistically significant difference was found in favour of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone. However, the difference is no more than marginal for this outcome in the category of non-serious/non-severe symptoms / late complications. This does not result in any 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

Outcomes on health-related quality of life were recorded with the scales of the EORTC QLQ-C30. In each case, time to deterioration by ≥ 10 points (scale range 0 to 100) was analysed.

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 both of these 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.

Side effects

Serious adverse events (SAEs)

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

Severe AEs

For the outcome of severe AEs, a statistically significant difference was found to the disadvantage of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone. This resulted in a hint of greater harm from daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone.

Discontinuation due to AEs (at least 1 drug component)

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

Infusion-related reaction

The analyses submitted by the company for the outcome of infusion-related reaction are unsuitable for the benefit assessment. However, the symptomatic events underlying the infusion-related reactions have been recorded as specific AEs.

Further specific AEs

For each of the outcomes of skin and subcutaneous tissue disorders (System Organ Class [SOC], severe AEs) and anaemia (Preferred Term [PT], severe AEs), a statistically significant difference was found in favour of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone. For these 2 specific AEs, there is therefore a

hint of lesser harm from daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone. However, it is questionable whether the effect on the outcome of anaemia (PT, severe AEs) is actually to be ascribed to the side effects category 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, severe AEs), 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 from 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 the extent of the added benefit of the drug daratumumab compared with the ACT is assessed as follows:

All things considered, both favourable and unfavourable effects of different extents were found for daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone.

In terms of the favourable effects, added benefit of considerable extent was found for both the outcome of overall survival and the symptom of pain. Further, there is an added benefit for 2 out of 6 health-related quality of life scales, each with the extent of minor, as well as 2 specific AEs, with an extent of considerable.

The unfavourable effects apply exclusively to outcomes of the side effects category (total rate of severe AEs with considerable extent as well as 4 specific AEs, most with considerable extent).

All things considered, favourable effects in 4 outcome categories, 3 of which with an extent of considerable, are hence offset by unfavourable effects in the side effects category, of largely considerable extent. Overall, the favourable effects outweigh the unfavourable ones.

[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].

In summary, there is a hint of considerable added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone for adults 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 + lenalidomide + dexamethasone in comparison with the ACT.

Table 3: Daratumumab in combination with lenalidomide and 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 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**	Hint of considerable added benefit
a. Presented is 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 of 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 research question presented in Table 4 results from the ACT specified by the G-BA.

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

Therapeutic indication	**ACT[a]**
Adult patients with newly diagnosed multiple myeloma who are ineligible for autologous 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. Presented is 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 of 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 listed 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 the added benefit.

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on daratumumab (status: 7 September 2021)
- bibliographical literature search on daratumumab (last search on 7 September 2021)
- Search in trial registries / study results databases on daratumumab (last search on 10 September 2021)
- Search on the G-BA website on daratumumab (last search on 6 August 2021)

To check the completeness of the study pool:

- search in trial registries for studies on daratumumab (last search on 14 October 2021); for search strategies, see Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

2.3.1 Studies included

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

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

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (CSR) (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
54767414MMY3008 (MAIA[d])	Yes	Yes	No	Yes [3-6]	Yes [7,8]	Yes [9-14]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the tables below, the study will be referred to by this acronym.

RCT: randomized controlled trial

The MAIA study was used for the benefit assessment. However, there are uncertainties with regard to the included patients' ineligibility for ASCT. Due to these uncertainties, at most hints, e.g. of added benefit, can be derived from the MAIA study (see Section 2.4.2). The reasoning is provided in the sections below.

Suitability of autologous stem cell transplantation for the study population

It is unclear whether the patients included in the MAIA study were in fact ineligible for high-dose chemotherapy with subsequent ASCT, as required in the therapeutic indication. According to the study's inclusion criteria, both patients 65 years of age or older and patients under 65 years of age with important comorbidities were deemed ineligible for ASCT. At the time the study was being 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 were changed. Since that time, biological age and good general health are deemed more important than chronological age [15-18]. It is difficult to define a maximum age for ASCT therapy. Rather, the suitability of ASCT is to be assessed individually for each patient, taking into account general health, any comorbidities, and organ function.

Consequently, according to 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 selected inclusion criterion of age ≥ 65 years (without further consideration of general health) might have led to the inclusion of patients who would have been eligible for ASCT and who are therefore not in the population of the therapeutic indication to be assessed. As part of the marketing authorization procedure, the European Medicines Agency (EMA) likewise requested additional data (AEs) on 1 subpopulation defined post hoc whose characteristics strongly suggest that ASCT is not a suitable treatment option: age ≥ 75 years and age 65 to 74 years with important comorbidities and/or fair general health (e.g. ECOG-PS = 2) [19]. In the context of the marketing authorization procedure, the company consequently defined post hoc the following 2 subpopulations :

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

Populations submitted by the company for the benefit assessment

As it did in the dossier for the prior assessment of daratumumab in combination with lenalidomide and dexamethasone [12], the company submitted in the dossier for the present assessment data on the above-described subpopulation 1 of 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 used the results of the MAIA study's total population. For the subgroup analyses, the company used the "ASCT-ineligible" subpopulation. The company justifies this approach by stating that the results of the total population are comparable to those of the subpopulation, and furthermore, no differences in effects were found in the subgroup analysis ("ASCT-eligible" versus "ASCT-ineligible"). In addition, the company used analyses of German health services data to determine whether according to current criteria [20,21], the study population should still be deemed ineligible for ASCT. On the basis of these data, the company concludes that the portion of the MAIA study population who might be eligible for ASCT equals roughly 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. The

uncertainty regarding the definition of the population ineligible for ASCT is further underscored by the fact that the marketing authorization procedure took into account data for 2 subpopulations with different ASCT ineligibility criteria (see above). According to guideline recommendations, ineligibility for ASCT should be determined individually for each patient, without regard to chronological age. Such determination was not performed in this form in the MAIA study, and it is impossible to collect the required data post hoc (e.g. due to missing comorbidity data). However, comparing the results of the "ASCT-ineligible" subpopulation versus the total population at the now available 3rd data cut-off shows, like the 2nd data cut-off [12], that the effect size is very similar for each of the decision-relevant outcomes. The EMA as well based its recommendation for approval only on the overall population [22]. Concurring with the company's approach, this benefit assessment is therefore based on the results of the overall population. 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. Since no consequences arise from the results of the "ASCT-ineligible" subpopulation for the benefit assessment, the results on the 3rd data cut-off are not provided as a supplementary presentation. The results of the "ASCT ineligible" subpopulation are found in the company's Module 4 A.

2.3.2 Study characteristics

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

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
MAIA	RCT, open-label, parallel	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 < 65 years of age in the presence of important comorbidities) ▪ ECOG-PS ≤ 2	Daratumumab + lenalidomide + dexamethasone (N = 368) Lenalidomide + dexamethasone (N = 369)	Screening: ≤ 21 days before randomization Treatment: Until disease progression, unacceptable toxicity, consent withdrawal, or study end[b] Follow-up observation[c]: Outcome-specific, at the longest until death, consent withdrawal, or study end[b]	176 study centres in Australia, Austria, Belgium, Canada, Denmark, France, Germany, Great Britain, Ireland, Israel, Italy, Netherlands, Sweden, United States 03/2015–ongoing 1st data cut-off: 24/09/2018 2nd data cut-off: 10/06/2019 3rd data cut-off: 19/02/2021	Primary: PFS Secondary: overall survival, health status, symptoms, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. The study will end 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 disease progression are followed up until confirmed disease progression, subsequent anti-myeloma therapy, consent withdrawal, 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: Characteristics of the intervention – RCT, direct comparison: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone (multipage table)

Study	Intervention	Comparison
MAIA	Daratumumab: 16 mg/kg BW 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 creatinine clearance 30–50 mL/min +	Lenalidomide: from Cycle 1, daily (Days 1–21) ▪ 25 mg orally at a creatinine clearance > 50 mL/min ▪ 10 mg orally at 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 takes 4 weeks	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 takes 4 weeks
	Treatment adjustments ▪ Daratumumab: dose modifications not allowed[a] ▪ Lenalidomide, dexamethasone: according to the study protocol, dose reduction or drug discontinuation was allowed. ▪ Patients who discontinue a single component of their treatment regimens are allowed to continue the treatment with the remaining components.	
	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-adrenergic receptor agonist (e.g. salbutamol) ▪ Medication to control the respective respiratory disease (e. g. inhaled corticosteroids, long-acting bronchodilators)	

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

Study	Intervention	Comparison
	Concomitant treatment **Allowed** ▪ During the study, all drugs and therapies deemed necessary for supportive therapy were allowed (except disallowed concomitant treatments as listed 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 Cycle 1) ▪ Therapy for tumour lysis syndrome ▪ Infection prophylaxis (e. g. Pneumocystis carinii prevention, herpes zoster prevention) **Disallowed** ▪ Other antineoplastic myeloma therapies ▪ Systemic corticosteroids (> 10 mg prednisone/day or equivalent) – except in case of infusion-related side effects – 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.

BMI: body mass index ; BW: body weight; 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 ongoing.

The study included adults (≥ 18 years of age) with newly diagnosed multiple myeloma who were ineligible for high-dose chemotherapy with subsequent ASCT. In addition, patients had to have an ECOG PS of 0 to 2 as a measure of general health. In accordance with the inclusion criteria, patients were deemed ineligible for ASCT if they were either 65 years of age or older or were under 65 years and had important comorbidities. Since eligibility for ASCT had not been determined on an individual patient level, it is possible that patients who would in fact have been eligible for ASCT were included in the study. Despite this uncertainty, the results of the MAIA study's total population were used for this benefit assessment (see Section 2.3.1 for the reasoning).

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, 368 to the intervention arm receiving daratumumab + lenalidomide + dexamethasone and 369 to the comparator arm receiving lenalidomide + dexamethasone.

Treatment in both study arms was provided until disease progression, unacceptable toxicity, withdrawal of consent, or until the end of study. The drugs were administered largely in

accordance with the specifications in the SPC [23,24]. 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-offs

A total of 3 data cut-offs are available for the MAIA study:

- Data cut-off 24 September 2018: predefined interim analysis after reaching 234 events concerning the primary outcome
- Data cut-off 10 June 2019: data cut-off requested by the EMA
- Data cut-off 19 February 2021: predefined interim analysis after reaching 273 events concerning the outcome of overall survival

Due to new scientific evidence having become available, the data cut-off of 19 February 2021 was used for the present benefit assessment.

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

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

Study **Outcome category** **Outcome**	**Planned follow-up observation**
MAIA	
Mortality	
Overall survival	Until study end, death, or consent withdrawal (whichever is earlier)
Morbidity	
Symptoms / health status (EORTC QLQ-C30, EQ-5D-VAS)	For 16 weeks after start of disease progression
Health-related quality of life (EORTC QLQ-C30)	For 16 weeks after start of disease progression
Side effects	
All outcomes in the side effects category	For 30 days after the last administration of the study drug or until consent withdrawal or until the start of subsequent anti-myeloma therapy (whichever is earlier)
EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; RCT: randomized controlled trial; VAS: visual analogue scale	

The follow-up periods for the outcomes of morbidity, health-related quality of life, and side effects are systematically shortened. For instance, outcomes from the side effects category were

collected only for 30 days after 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 on the total study period or the time to patient death, it would be necessary to record these outcomes as well for the total period, as was done for survival.

Table 9 shows the patient characteristics of the included study.

Table 9: Characteristics of the study populations – RCT, direct comparison: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone (multipage 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)	4 (1)
65 to < 70 years, n (%)	74 (20)	73 (20)
70 to < 75 years, n (%)	130 (35)	131 (36)
≥ 75 years, n (%)	160 (44)	161 (44)
Sex [f/m], %	49/51	47/53
Ancestry, n (%)		
White	336 (91)	339 (92)
Black, African American	12 (3)	16 (4)
Other[b]	9 (2)	9 (2)
Unknown / not reported[c]	11 (3)	5 (1)
ECOG PS, n (%)		
0	127 (35)	123 (33)
1	178 (48)	187 (51)
2	63 (17)	59 (16)
ISS[d], n (%)		
I	98 (27)	103 (28)
II	163 (44)	156 (42)
III	107 (29)	110 (30)
Disease duration: time from first diagnosis to randomization [months], mean (SD)	1.4 (1.5)	1.3 (1.4)
Number of osteolytic lesions, n (%)		
None	100 (27)	93 (25)
1–3	103 (28)	97 (26)
4–10	88 (24)	90 (24)
> 10	77 (21)	89 (24)

Table 9: Characteristics of the study populations – RCT, direct comparison: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone (multipage table)

Study Characteristics Category	Daratumumab + lenalidomide + dexamethasone N[a] = 368	Lenalidomide + dexamethasone N[a] = 369
Cytogenetic risk profile, n (%)[c]		
Standard risk	271 (85)	279 (86)
High risk	48 (15)	44 (14)
Treatment discontinuation[f], n (%[c])	209 (57)	298 (81)
Study discontinuation[g], n (%[c])	128 (35)	179 (49)

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. IQWiG calculations; includes Asian, Hawaiian and Pacific Islander, and patients of multiple ancestries.
c. IQWiG calculations.
d. ISS based on serum β2-microglobulin and albumin values.
e. Cytogenetic risk based on FISH or karyotyping; based on the following high-risk markers: del(17p), t(4;14), and t(14;16); determined for only 319 patients in the intervention arm and 323 patients in the control arm.
f. In both treatment arms, the most common reasons for treatment discontinuation were progression of the underlying illness (intervention arm 27%; comparator arm 34%) and AEs (intervention arm 13%; comparator arm 23%).
g. The most common reason for study drop-out was death (32% in intervention arm; 42% in comparator arm).

AE: adverse event; 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; RCT: randomized controlled trial; SD: standard deviation

Patient characteristics are balanced between the two MAIA treatment arms. Patients were 74 years of age on average and predominantly white (approximately 92%). Women represented almost 50% of patients in both study arms. The vast 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 (57% in the intervention arm versus 81% in the comparator arm). In both study arms, the most common reason for treatment discontinuation was disease progression.

Table 10 shows the mean and median patient treatment duration and the mean and median follow-up period 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]	47.5 [0.10; 69.26]	22.6 [0.03; 69.22]
Mean (SD)	26.97 (20.30)	39.00 (20.61)
Observation period [months]		
Overall survival	N = 368	N = 369
Median [min; max]	56.6 [0.03; 69.29]	55.9 [0.03; 69.52]
Mean (SD)	46.18 (18.00)	42.14 (19.01)
Morbidity, health-related quality of life	N = 368	N = 369
EQ-5D		
Median [min; max]	43.8 [ND]	22.8 [ND]
Mean (SD)	ND	ND
EORTC QLQ C-30:		
Median [min; max]	44.6 [ND]	22.8 [ND]
Mean (SD)	ND	ND
Side effects	N = 364	N = 365
Median [min; max]	48.5 [ND]	23.5 [ND]
Mean (SD)	ND	ND

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

In the MAIA study, the median treatment duration is longer in the intervention arm than in the comparator arm (median: 47.5 versus 22.6 months). The median observation period for the outcome of overall survival is comparable between the treatment arms. Since the follow-up observation for the outcomes of the morbidity, health-related quality of life, and side effects categories are linked to treatment duration (see Table 8), the median follow-up observation for these outcomes is likewise (about twice) longer in the intervention arm than in the comparator arm.

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

Table 11: Information on antineoplastic subsequent therapies – RCT, direct comparison: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone (multipage table)

Study **Drug class** **Drug**	**Patients with subsequent therapy n (%)**	
	Daratumumab + lenalidomide + dexamethasone **N = 364**	**Lenalidomide + dexamethasone** **N = 365**
MAIA (data cut-off 19 February 2021)		
Total (patients with ≥ 1 subsequent therapy	114 (31.3)	186 (51.0)
≥ 1 autologous stem cell transplantation	3 (0.8)	6 (1.6)
Other antineoplastic drugs	102 (28.0)	166 (45.5)
Bortezomib	81 (22.3)	141 (38.6)
Daratumumab	17 (4.7)	85 (23.3)
Carfilzomib	17 (4.7)	37 (10.1)
Ixazomib	11 (3.0)	20 (5.5)
Elotuzumab	4 (1.1)	7 (1.9)
Monoclonal antibodies	3 (0.8)	2 (0.5)
Venetoclax	3 (0.8)	1 (0.3)
Isatuximab	2 (0.5)	1 (0.3)
Rituximab	2 (0.5)	1 (0.3)
Panobinostat	1 (0.3)	1 (0.3)
Carboplatin	0 (0)	1 (0.3)
Cisplatin	1 (0.3)	0 (0)
Nivolumab	0 (0)	1 (0.3)
Oxaliplatin	1 (0.3)	0 (0)
Vemurafenib	0 (0)	1 (0.3)
Alkylating drugs	58 (15.9)	96 (26.3)
Cyclophosphamide	42 (11.5)	65 (17.8)
Melphalan	20 (5.5)	42 (11.5)
Bendamustine	6 (1.6)	6 (1.6)
Cytotoxic antibiotics and related substances	8 (2.2)	3 (0.8)
Doxorubicin	8 (2.2)	3 (0.8)
Vegetable alkaloids and other natural substances	5 (1.4)	5 (1.4)
Vincristine	2 (0.5)	3 (0.8)
Etoposide	3 (0.8)	1 (0.3)
Docetaxel	0 (0)	1 (0.3)
Antimetabolites	2 (0.5)	0 (0)
Azacitidine	1 (0.3)	0 (0)
Fluoruracil	1 (0.3)	0 (0)

Table 11: Information on antineoplastic subsequent therapies – RCT, direct comparison: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone (multipage table)

Study **Drug class** **Drug**	**Patients with subsequent therapy n (%)**	
	Daratumumab + lenalidomide + dexamethasone **N = 364**	**Lenalidomide + dexamethasone** **N = 365**
Investigational antineoplastic drugs	0 (0)	1 (0.3)
Systemic corticosteroids	99 (27.2)	164 (44.9)
Dexamethasone	93 (25.5)	150 (41.1)
Prednisone	16 (4.4)	32 (8.8)
Prednisolone	3 (0.8)	8 (2.2)
Methylprednisolone	2 (0.5)	3 (0.8)
Immunosuppressants	75 (20.6)	102 (27.9)
Pomalidomide	52 (14.3)	66 (18.1)
Lenalidomide	31 (8.5)	39 (10.7)
Thalidomide	3 (0.8)	8 (2.2)
Antibacterials for systemic use	2 (0.5)	1 (0.3)
Clarithromycin	1 (0.3)	1 (0.3)
Doxycycline	1 (0.3)	0 (0)
Other therapeutic products	1 (0.3)	0 (0)
Folic acid	1 (0.3)	0 (0)
Investigational preparations	1 (0.3)	0 (0)

n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial

In both study arms, starting subsequent anti-myeloma therapy was allowed after confirmed disease progression. There were no restrictions regarding the type of subsequent therapy: the choice of subsequent anti-myeloma therapy was at the discretion of the treating physician. At the data cut-off date of 19 February 2021, the proportion of patients with ≥ 1 subsequent therapy was lower in the intervention arm than in the comparator arm (31.3% versus 51.0%).

Pursuant to the study protocol, patients in the comparator arm had the option of receiving subsequent daratumumab therapy as locally approved. Daratumumab as subsequent therapy was received by 17 patients in the intervention arm (4.7%) and 85 patients in the comparator arm (23.3%). Nine patients received ASCT as subsequent therapy.

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 (at study level) – RCT, direct comparison: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone

Study	Adequate random sequence generation	Allocation concealment	Blinding		Nonselective reporting	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
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.

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

Transferability of the study results to the German health care 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 is 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, in consideration of the uncertainty associated with the transferability of clinical data.

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

2.4 Results on added benefit

2.4.1 Outcomes included

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

- Mortality
  - Overall survival
- Morbidity
  - Health status measured using the EQ-5D visual analogue scale (VAS)
  - Symptoms recorded with the EORTC QLQ-C30
- Health-related quality of life
  - Health-related quality of life, recorded with the EORTC QLQ-C30

- Side effects
  - SAEs
  - Severe AEs (CTCAE grade ≥ 3)
  - Discontinuation due to AEs (at least one drug component)
  - Infusion-related reaction
  - Further specific AEs, if any

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

Table 13 shows the outcomes for which 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)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs[b]	Infusion-related reaction	Other specific AEs[a,c]
MAIA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[d]	Yes

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. Operationalized as discontinuation of at least 1 drug component.
c. The following events were assessed (MedDRA coding): chills (PT, AEs), respiratory, thoracic and mediastinal disorders (SOC, AEs), infections and infestations (SOC, SAEs), neutropenia (PT, severe AEs), and skin and subcutaneous tissue disorders (SOC, severe AEs).
d. The analysis presented by the company is unsuitable for the benefit assessment, but the events underlying the outcome are recorded via the specific AEs. See the below section of the present benefit assessment for the reasoning.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

- Health status, surveyed with EQ-5D VAS, as well as symptoms and health-related quality of life, surveyed with the scales of EORTC QLQ-C30: For health status, symptoms, and health-related quality of life outcomes, the company submitted responder analyses using the following response criteria:

- Health status (EQ-5D VAS): time to deterioration or improvement by ≥ 7, ≥ 10 and ≥ 15 points (scale range 0 to 100).
- Symptoms (EORTC QLQ-C30) and health-related quality of life (EORTC QLQ-C30): time to deterioration or improvement by ≥ 10 points (scale range 0 to 100).

As explained in the IQWiG General Methods [1,25], for a response criterion to reflect with sufficient certainty a change noticeable for the patient, it should correspond to a predefined value of at least 15% of the scale range of an instrument (in post hoc analyses, exactly 15% of the scale range). To derive added benefit for the outcome of health status (EQ-5D VAS), time to deterioration by ≥ 15 points is therefore used. The analyses with the response criteria ≥ 7 and ≥ 10 points are presented as supplementary information in Appendix D of the full dossier assessment.

For EORTC QLQ-C30 and its supplementary modules, the analysis with the previously accepted response threshold of 10 points was, in certain constellations, viewed as a sufficient approximation to an analysis with a 15% threshold (15 points) and was used for the benefit assessment (for an explanation, see dossier assessment A20-97 [26]). Regardless of this, for a transitional period until the adjusted module templates for the dossier come into force (see FAQs of the G-BA [27]), analyses with the previously accepted response threshold of 10 points for the EORTC QLQ-C30 as well as all additional modules of the EORTC will be used primarily.

Time to deterioration is used for each of the outcomes of health status (EQ-5D VAS), symptoms (EORTC QLQ-C30), and health-related quality of life (EORTC QLQ-C30). Given the progressive course of disease to be expected in the present therapeutic indication and particularly taking into account the distribution of absolute scale values at baseline, an analysis of deterioration of health status is of primary relevance in the present benefit assessment. Since the company has not provided any detailed information on the operationalization of deterioration, the latter is assumed to be time to first deterioration. According to the statistical analysis plan, time to deterioration was predefined via a response criterion determined through distribution-based approaches. The plan defined death due to progression as a deterioration. However, Module 4 A's operationalization of deterioration does not suggest that the analyses included death as an event.

- Infusion-related reaction: The analyses presented by the company on the outcome of infusion-related reaction are unsuitable for the benefit assessment. In the MAIA study's case report form, infusion-related reactions were documented as events related to the infusion of daratumumab. However, since no placebo infusions were administered in the comparator arm, these events can occur only in the intervention arm. This renders a comparison between study arms impossible for this outcome. The Facon 2019 publication [10] shows, for the 1st data cut-off, the events included in the analyses presented by the company on the outcome of infusion-related reaction.

  In the MAIA study, the events underlying the outcome of infusion-related reaction are additionally included in the analyses of AEs (total rates and specific AEs). Some specific

AEs can be inferred to constitute infusion-related reactions since (1) they are plausible symptoms of cytokine release syndrome (e.g. PT chills; PTs dyspnoea, coughing and bronchospasm from system organ class [SOC] respiratory, thoracic and mediastinal disorders) and (2) they typically occur early at the time of the first infusion with daratumumab (see Kaplan-Meier curves in Appendix B of the full dossier assessment). Where a statistically significant difference between treatment groups is found for these specific AEs and the frequency thresholds shown in Appendix C of the full dossier assessment are exceeded, the events underlying the outcome of infusion-related reaction are therefore depicted by specific AEs in this benefit assessment (see Table 15).

The type of survey and analysis used in the MAIA study is preferable to the approach used in other studies (see, e.g., dossier assessment A21-61 [28]), where the events underlying the outcome of infusion-related reaction are not included in AEs. This allows taking these events into account in the benefit assessment even if they occurred in unblinded studies comparing orally and intravenously administered drugs. However, to obtain a complete picture of infusion-related reactions, an additional aggregated analysis of these specific AEs (e.g. by means of a predefined PT list) including all events, regardless of frequency or statistic significance, would be desirable.

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 across outcomes and outcome-specific risk of bias – RCT, direct comparison: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone

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

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. Operationalized as discontinuation of at least 1 drug component.
c. The following events were assessed (MedDRA coding): chills (PT, AEs), respiratory, thoracic and mediastinal disorders (SOC, AEs), infections and infestations (SOC, SAEs), neutropenia (PT, severe AEs), and skin and subcutaneous tissue disorders (SOC, severe AEs).
d. Lack of blinding in subjective recording of outcomes.
e. Incomplete observations for potentially informative reasons with different follow-up observations.
f. Substantial proportion of patients (> 10%) not taken into account in the analysis.
g. The analysis presented by the company is unsuitable for the benefit assessment, but the events underlying the outcome are recorded through the specific AEs. See Section 2.4.1 of the present benefit assessment for the reasoning.
h. Missing blinding with potentially subjective recording of outcomes for selected specific AEs.

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

The risk of bias for the result on the outcome of overall survival was rated as low.

For each of the outcomes on symptoms (EORTC QLQ-C30), health-related quality of life (EORTC QLQ-C30), and health status (EQ-5D VAS), the risk of bias of results is rated as high due to lack of blinding with subjective recording of outcomes. This rating is further supported by the fact that regarding the outcomes on health status, symptoms, and health-related quality of life, the planned repeated measurements over time are incomplete for a considerable percentage of patients and that this was due to potentially informative reasons, such as treatment discontinuation due to progression.

For the outcome of severe AEs, the risk of bias of the result was rated as low: Firstly, events occurred in a substantial percentage of patients (approximately 96% of patients in the intervention arm and approximately 89% of patients in the control arm), and in the majority of these patients, they furthermore occurred at an early time point after randomization. Secondly, censoring did not occur to a relevant extent in the first months, in which the Kaplan-Meier

curves already showed discrepancies (Figure 18). Therefore, there is no increased risk of bias in the estimated hazard ratio due to potentially informative censoring.

In comparison with severe AEs, SAEs were less common and occurred later; therefore, over the entire course of the study, a considerable proportion of patients might have received incomplete follow-up for potentially informative reasons. Therefore, the risk of bias for this outcome was rated as high. Due to lack of blinding with subjective recording of outcomes, the risk of bias of the outcome of discontinuation due to AEs is also rated as high.

Due to incomplete follow-up for potentially informative reasons, the results of the MAIA study's specific AEs of chills (PT, AEs), respiratory, thoracic, and mediastinal disorders (SOC, AEs), infections and infestations (SOC, SAEs), skin and subcutaneous tissue disorders (SOC, severe AEs), neutropenia (PT, severe AEs), and anaemia (PT, severe AEs) are likewise deemed to have a high risk of bias. 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.

Overall assessment of the certainty of conclusions

Irrespective of the aspects described for the risk of bias, the certainty of conclusions of study results is reduced for the present research question due to the uncertainties described in Section 2.3.1 regarding ASCT ineligibility of included patients. Overall, at most hints, e.g. of an added benefit, can therefore be derived on the basis of the MAIA study.

2.4.3 Results

Table 15 summarizes the results of the comparison of daratumumab + lenalidomide + dexamethasone versus lenalidomide + dexamethasone for adult patients with newly diagnosed multiple myeloma who are ineligible for ASCT. Where necessary, calculations conducted by IQWiG are provided in addition to the data from the company's dossier. The Kaplan-Meier curves on the included outcomes are presented in Appendix B of the full dossier assessment, and the results on common AEs, SAEs, severe AEs, and discontinuations due to AEs can be found in Appendix C of the full dossier assessment.

Table 15: Results (mortality, morbidity, quality of life, side effects) – RCT, direct comparison: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone (multipage 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 19 February 2021)					
Mortality					
Overall survival	368	NR 117 (31.8)	369	NR [55.69; NC] 156 (42.3)	0.68 [0.53; 0.86]; 0.001
Morbidity					
Health status					
EQ-5D VAS[b]	368	53.26 [39.23; NC] 146 (39.7)	369	39.62 [30.09; 53.49] 127 (34.4)	0.92 [0.72; 1.17]; 0.477
EORTC QLQ-C30[c]					
Fatigue	368	4.86 [4.70; 7.52] 237 (64.4)	369	4.80 [4.63; 7.49] 225 (61.0)	0.85 [0.71; 1.02]; 0.086
Nausea and vomiting	368	38.70 [26.68; NC] 159 (43.2)	369	30.55 [21.32; 53.49] 145 (39.3)	0.92 [0.73; 1.16]; 0.478
Pain	368	39.42 [27.20; 54.51] 164 (44.6)	369	17.97 [10.78; 27.27] 168 (45.5)	0.69 [0.56; 0.86]; < 0.001
Dyspnoea	368	29.01 [21.22; 40.84] 185 (50.3)	369	15.74 [10.25; 22.08] 177 (48.0)	0.78 [0.63; 0.96]; 0.019
Insomnia	368	16.92 [10.15; 29.18] 196 (53.3)	369	16.46 [10.19; 27.76] 171 (46.3)	0.94 [0.77; 1.16]; 0.588
Appetite loss	368	40.28 [27.66; NC] 162 (44.0)	369	26.02 [11.53; 32.26] 161 (43.6)	0.81 [0.65; 1.01]; 0.056
Constipation	368	21.68 [10.48; 33.77] 180 (48.9)	369	16.13 [7.72; 26.74] 173 (46.9)	0.84 [0.68; 1.04]; 0.117
Diarrhoea	368	15.70 [10.25; 16.33] 235 (63.9)	369	10.64 [9.96; 15.97] 211 (57.2)	0.95 [0.79; 1.15]; 0.627

Table 15: Results (mortality, morbidity, quality of life, side effects) – RCT, direct comparison: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone (multipage 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]
Health-related quality of life					
EORTC QLQ-C30[c]					
Global health status	368	26.78 [17.51; 39.79] 182 (49.5)	369	21.26 [11.37; 28.68] 167 (45.3)	0.87 [0.71; 1.08]; 0.213
Physical functioning	368	45.47 [27.76; NC] 162 (44.0)	369	21.52 [12.75; 33.51] 165 (44.7)	0.77 [0.62; 0.96]; 0.022
Role functioning	368	10.22 [7.33; 18.17] 209 (56.8)	369	10.19 [6.80; 15.70] 193 (52.3)	0.92 [0.76; 1.12]; 0.411
Emotional functioning	368	46.09 [32.59; NC] 156 (42.4)	369	32.23 [16.53; 45.60] 144 (39.0)	0.84 [0.67; 1.06]; 0.146
Cognitive functioning	368	7.98 [7.42; 15.70] 237 (64.4)	369	10.15 [7.52; 11.56] 200 (54.2)	0.95 [0.78; 1.14]; 0.565
Social functioning	368	10.68 [7.49; 21.19] 209 (56.8)	369	7.52 [4.83; 10.41] 203 (55.0)	0.82 [0.67; 0.99]; 0.045
Side effects					
AEs (supplementary information)	364	0.03 [NC] 364 (100)	365	0.20 [0.13; 0.26] 363 (99.5)	–
SAEs	364	12.85 [7.56; 16.46] 281 (77.2)	365	9.82 [7.62; 12.71] 257 (70.4)	0.93 [0.79; 1.11]; 0.434
Severe AEs[d]	364	0.72 [0.69; 1.08] 350 (96.2)	365	1.91 [1.64; 2.86] 324 (88.8)	1.37 [1.17; 1.60]; < 0.001
Discontinuation due to AEs[e]	364	40.44 [32.46; 48.16] 176 (48.4)	365	48.10 [37.88; NC] 131 (35.9)	1.18 [0.94; 1.48]; 0.162
Infusion-related reaction	Analysis unsuitable[f]				
Chills (PT, AEs)	364	NR 49 (13.5)	365	NR 6 (1.6)	8.07 [3.46; 18.86]; < 0.001
Respiratory, thoracic, and mediastinal disorders (SOC, AEs)[g]	364	4.63 [2.79; 7.29] 267 (73.4)	365	19.38 [12.71; 31.31] 179 (49.0)	1.82 [1.50; 2.20]; < 0.001
Infections and infestations (SOC, SAEs)	364	NR [45.60; NC] 149 (40.9)	365	NR 98 (26.8)	1.32 [1.02; 1.71]; 0.036
Neutropenia (PTs, severe AEs[d])	364	23.75 [12.95; 39.49] 197 (54.1)	365	NR [40.41; NC] 135 (37.0)	1.60 [1.28; 1.99]; < 0.001

Table 15: Results (mortality, morbidity, quality of life, side effects) – RCT, direct comparison: daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone (multipage 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]
Anaemia (PT, severe AEs[d])	364	NR 61 (16.8)	365	NR 79 (21.6)	0.61 [0.43; 0.85]; 0.004
Skin and subcutaneous tissue disorders (SOC, severe AEs[g])	364	NR 20 (5.5)	365	NR 35 (9.6)	0.51 [0.29; 0.88]; 0.016

a. HR, CI, and p-value: Cox proportional hazards model stratified by the factors of ISS stage, region, and age.
b. Time to first deterioration. A decrease in EQ-5D VAS by ≥ 15 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
c. Time to first deterioration. An EORTC QLQ-C30 increase (symptoms) or decrease (health-related quality of life) by ≥ 10 points from baseline is deemed a clinically relevant deterioration (scale range 0 to 100).
d. Operationalized as CTCAE grade ≥ 3.
e. Operationalized as discontinuation of at least 1 drug component.
f. The analysis presented by the company is unsuitable for the benefit assessment, but the events underlying the outcome are additionally recorded through the specific AEs. See Section 2.4.1 of the present dossier assessment for the reasoning.
g. Includes, among others, the PTs of coughing, dyspnoea, oropharyngeal pain, rhinorrhoea, wheezing, throat irritation, and bronchospasm.

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; EQ-5D: EuroQoL 5 Dimensions Questionnaire; 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; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes (see Sections 2.3.1 and 2.4.2 for the reasoning).

Mortality

Overall survival

For the outcome of all-cause survival, a statistically significant difference was found in favour of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone. This results in a hint of an added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone.

Morbidity

Health status (EQ-5D VAS)

For the outcome of health status, operationalized as time to EQ-5D VAS deterioration by ≥ 15 points (scale range 0 to 100), 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 for this outcome.

Symptoms (EORTC QLQ-C30)

Symptom outcomes were recorded using the EORTC QLQ-C30 scales. In each case, time to deterioration by ≥ 10 points (scale range 0 to 100) was analysed.

For the outcome of pain, a statistically significant difference was found in favour of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone. This results in a hint of an added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone.

For the outcome of dyspnoea, a statistically significant difference was found in favour of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone. However, the difference 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 (see Section 2.5.1).

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

Outcomes on health-related quality of life were recorded with the scales of the EORTC QLQ-C30. In each case, time to deterioration by ≥ 10 points (scale range 0 to 100) was analysed.

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.

No statistically significant difference between treatment arms was found for any of the outcomes of global health status, role functioning, emotional functioning, and cognitive

functioning. 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.

Side effects

SAEs

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

Severe AEs

For the outcome of severe AEs, a statistically significant difference was found to the disadvantage of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone. This results in a hint of greater harm from daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone.

Discontinuation due to AEs (at least 1 drug component)

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

Infusion-related reaction

The analyses submitted by the company for the outcome of infusion-related reaction are unsuitable for the benefit assessment (see Section 2.4.1). However, the events underlying infusion-related reactions have been surveyed through the specific AEs.

Further specific AEs

Diseases of the skin and subcutaneous tissue (SOC, severe AEs), anaemia (PT, severe AEs)

For each of the outcomes of skin and subcutaneous tissue disorders (SOC, severe AEs) and anaemia (PT, severe AEs), a statistically significant difference was found in favour of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone. For these 2 specific AEs, there is therefore a hint of lesser harm from daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone. However, it is questionable whether the effect on the outcome of anaemia (PT, severe AEs) is actually to be ascribed to the side effects category 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, severe AEs)

For each of the outcomes of chills (PT, AEs), respiratory, thoracic, and mediastinal disorders (SOC, AEs), infections and infestations (SOC, SAEs), and neutropenia (PT, severe AEs), 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 from daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone.

2.4.4 Subgroups and other effect modifiers

For the MAIA study, no subgroup analyses were used in the benefit assessment. The reasons for this are as follows:

The MAIA study is relevant for the present research question. However, the results are subject to uncertainty with regard to the included population (patients ineligible for ASCT) (see Section 2.3.1). Any subsequent subgroup analyses would therefore be subject to additional uncertainty: It is unknown which potential subgroups patients still eligible for ASCT fall under 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 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.

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 16).

Determination of the outcome category for symptom outcomes

For the symptoms outcomes below, it cannot be inferred from the dossier whether they are serious/severe or non-serious/non-severe. The allocation of these outcomes is explained below.

Pain

In Module 4 A, the outcome of pain was operationalized by a worsening of pain by ≥ 10 points on the EORTC QLQ-C30 pain scale. In accordance with Module 4 A, 51% of patients received opioids before randomization or within a month after treatment start. According to the company, the percentage of patients who received opioids increased to 70% over the course of

the study. Due to the data submitted by the company in the previous procedure [12], information on patients' opioid use is available for the time briefly after study start as well as for other time points in the later course of the study. The data do not allow individually matching the specific time of opioid use with the time when pain worsened. However, the majority of patients received opioid pain therapy at multiple time points over the course of the study, and the percentage of these patients increased over the course of the study. Like in the prior assessment [12], therefore, the outcome of pain, surveyed with EORTC QLQ-C30, is allocated to the category of serious/severe symptoms / late complications.

Dyspnoea

For the outcome of dyspnoea, operationalized as deterioration in EORTC QLQ-C30 by ≥ 10 points, none of the available information would justify allocation as serious/severe symptoms / late complications. Therefore, this outcome was assigned to the outcome category of non-serious/non-severe symptoms / late complications.

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

Outcome category **Outcome**	**Daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone** **Median time to event (months)** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
Overall survival	NR vs. NR HR: 0.68 [0.53; 0.86] p = 0.001 Probability: hint	Outcome category: mortality $0.85 \leq CI_u < 0.95$ Added benefit; extent: considerable
Morbidity		
Health status (EQ-5D VAS; deterioration ≥ 15 points)		
EQ-5D VAS	53.26 vs. 39.62 HR: 0.92 [0.72; 1.17] p = 0.477	Lesser/added benefit not proven
Symptoms (EORTC QLQ-C30, deterioration ≥ 10 points)		
Fatigue	4.86 vs. 4.80 HR: 0.85 [0.71; 1.02] p = 0.086	Lesser/added benefit not proven
Nausea and vomiting	38.70 vs. 30.55 HR: 0.92 [0.73; 1.16] p = 0.478	Lesser/added benefit not proven
Pain	39.42 vs. 17.97 HR: 0.69 [0.56; 0.86] p < 0.001 Probability: hint	Outcome category: serious/severe symptoms / late complications $0.75 \leq CI_u < 0.90$ Added benefit; extent: considerable
Dyspnoea	29.01 vs. 15.74 HR: 0.78 [0.63; 0.96] p = 0.019	Lesser/added benefit not proven[c]
Insomnia	16.92 vs. 16.46 HR: 0.94 [0.77; 1.16] p = 0.588	Lesser/added benefit not proven
Appetite loss	40.28 vs. 26.02 HR: 0.81 [0.65; 1.01] p = 0.056	Lesser/added benefit not proven
Constipation	21.68 vs. 16.13 HR: 0.84 [0.68; 1.04] p = 0.117	Lesser/added benefit not proven
Diarrhoea	15.70 vs. 10.64 HR: 0.95 [0.79; 1.15] p = 0.627	Lesser/added benefit not proven

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

Outcome category **Outcome**	**Daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone** **Median time to event (months)** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Health-related quality of life (EORTC QLQ-C30, deterioration ≥ 10 points)		
Global health status	26.78 vs. 21.26 HR: 0.87 [0.71; 1.08] p = 0.213	Lesser/added benefit not proven
Physical functioning	45.47 vs. 21.52 HR: 0.77 [0.62; 0.96] p = 0.022 Probability: hint	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Added benefit; extent: minor
Role functioning	10.22 vs. 10.19 HR: 0.92 [0.76; 1.12] p = 0.411	Lesser/added benefit not proven
Emotional functioning	46.09 vs. 32.23 HR: 0.84 [0.67; 1.06] p = 0.146	Lesser/added benefit not proven
Cognitive functioning	7.98 vs. 10.15 0.95 [0.78; 1.14] p = 0.565	Lesser/added benefit not proven
Social functioning	10.68 vs. 7.52 HR: 0.82 [0.67; 0.99] p = 0.045 Probability: hint	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Added benefit; extent: minor
Side effects		
SAEs	12.85 vs. 9.82 HR: 0.93 [0.79; 1.11] p = 0.434	Greater/lesser harm not proven
Severe AEs	0.72 vs. 1.91 HR: 1.37 [1.17; 1.60] HR: 0.73 [0.63; 0.85][d] p < 0.001 Probability: hint	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Greater harm; extent: considerable
Discontinuation due to AEs	40.44 vs. 48.10 HR: 1.18 [0.94; 1.48] p = 0.162	Greater/lesser harm not proven
Infusion-related reaction	Analysis unsuitable[e]	Greater/lesser harm not proven

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

Outcome category **Outcome**	**Daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone** **Median time to event (months)** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Chills (UE)	NR vs. NR HR: 8.07 [3.46; 18.86] HR: 0.12 [0.05; 0.29][d] p < 0.001 Probability: hint	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm; extent: considerable
Respiratory, thoracic, and mediastinal disorders (AE)	4.63 vs. 19.38 HR: 1.82 [1.50; 2.20] HR: 0.55 [0.45; 0.67][d] p < 0.001 Probability: hint	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm; extent: considerable
Infections and infestations (SAEs)	NR vs. NR HR: 1.32 [1.02; 1.71] HR: 0.76 [0.58; 0.98][d] p = 0.036 Probability: hint	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Greater harm; extent: minor
Neutropenia (severe AE)	23.75 vs. NR HR: 1.60 [1.28; 1.99]; HR: 0.63 [0.50; 0.78][d] p < 0.001 Probability: hint	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Greater harm; extent: considerable
Anaemia (severe AEs)	NR vs. NR HR: 0.61 [0.43; 0.85] p = 0.004 Probability: hint	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Lesser harm; extent: considerable
Skin and subcutaneous tissue disorders (severe AE)	NR vs. NR HR: 0.51 [0.29; 0.88] p = 0.016 Probability: hint	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Lesser harm; extent: considerable

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
d. IQWiG calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
e. The analyses presented by the company are unsuitable for the benefit assessment, but the events underlying the outcome have been recorded through the specific AEs. See Section 2.4.1 of the present dossier assessment for the reasoning.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D: EuroQoL 5 Dimensions Questionnaire; HR: hazard ratio; NR: not reached; SAE: serious adverse event; VAS: visual analogue scale

2.5.2 Overall conclusion on added benefit

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

Table 17: Favourable and unfavourable effects from the assessment of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone

Favourable effects	**Unfavourable effects**
Mortality ▪ Overall survival: hint of an added benefit – extent: considerable	–
Serious/severe symptoms / late complications ▪ Pain: hint of an added benefit – extent: considerable	–
Health-related quality of life ▪ physical functioning, social functioning: each hint of an added benefit – extent: minor	–
Serious/severe side effects ▪ Anaemia (severe AEs)[a]; skin and subcutaneous tissue disorders (severe AEs): each hint of lesser harm – extent: considerable	Non-serious/non-severe side effects ▪ Chills (AEs); respiratory, thoracic, and mediastinal disorders (AEs): each hint of greater harm – extent: considerable Serious/severe side effects ▪ Severe AEs: hint of greater harm – extent: considerable ▫ Neutropenia (severe AEs): hint of greater harm – extent: considerable ▪ infections and infestations (SAEs): hint of greater harm – extent: minor
a. It is questionable whether the effect is actually to be ascribed to the side effects category or whether it rather reflects the clinical picture of the underlying disease. AE: adverse event; SAE: serious adverse event	

All things considered, both favourable and unfavourable effects of different extents were found for daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone.

In terms of the favourable effects, added benefit of considerable extent was found for both the outcome of overall survival and the symptom of pain. Further, there is an added benefit for 2 out of 6 health-related quality of life scales, each with the extent of minor, as well as for 2 specific AEs, with an extent of considerable.

The unfavourable effects apply exclusively to outcomes of the side effects category (total rate of severe AEs with considerable extent as well as 4 specific AEs, most with considerable extent).

All things considered, favourable effects in 4 outcome categories, 3 of which with an extent of considerable, are hence offset by unfavourable effects in the side effects category, of largely considerable extent. Overall, the favourable effects outweigh the unfavourable ones.

In summary, there is a hint of considerable added benefit of daratumumab + lenalidomide + dexamethasone in comparison with lenalidomide + dexamethasone for adults with newly diagnosed multiple myeloma who are ineligible for ASCT.

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

Table 18: Daratumumab in combination with lenalidomide and 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 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**	Hint of considerable added benefit
a. Presented is 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 of the company is printed in bold. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

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

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

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. Institute for Quality and Efficiency in Health Care. General Methods; Version 6.0 [online]. 2020 [Accessed: 22.03.2021]. URL: https://www.iqwig.de/methoden/general-methods_version-6-0.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://dx.doi.org/10.1002/bimj.201300274.

3. Janssen Research & Development. A phase 3 study comparing daratumumab, lenalidomide, and dexamethasone (DRd) vs lenalidomide and dexamethasone (Rd) in subjects with previously untreated multiple myeloma who are ineligible for high dose therapy: study 54767414MMY3008; clincal study report [unpublished]. 2019.

4. Janssen Research & Development. A phase 3 study comparing daratumumab, lenalidomide, and dexamethasone (DRd) vs lenalidomide and dexamethasone (Rd) in subjects with previously untreated multiple myeloma who are ineligible for high dose therapy: study 54767414MMY3008; Dokument zum 2. Datenschnitt 10.06.2019 [unpublished]. 2019.

5. Janssen Research & Development. A phase 3 study comparing daratumumab, lenalidomide, and dexamethasone (DRd) vs lenalidomide and dexamethasone (Rd) in subjects with previously untreated multiple myeloma who are ineligible for high dose therapy: study 54767414MMY3008; Abbreviated Clincal Study Report; Interim Analysis; Data Cutoff 19 February 2021, Zusatzanalysen [unpublished]. 2021.

6. Janssen Research & Development. A phase 3 study comparing daratumumab, lenalidomide, and dexamethasone (DRd) vs lenalidomide and dexamethasone (Rd) in subjects with previously untreated multiple myeloma who are ineligible for high dose therapy: study 54767414MMY3008; Abbreviated Clincal Study Report; Interim Analysis; Data Cutoff 19 February 2021 [unpublished]. 2021.

7. Janssen Research & Development. Study comparing daratumumab, lenalidomide, and dexamethasone with lenalidomide and dexamethasone in participants with previously untreated multiple myeloma [online]. 2021 [Accessed: 02.11.2021]. URL: https://ClinicalTrials.gov/show/NCT02252172.

8. Janssen-Cilag International. A phase 3 study comparing daratumumab, lenalidomide, and dexamethasone (DRd) vs lenalidomide and dexamethasone (Rd) in subjects with previously untreated multiple myeloma who are ineligible for high dose therapy [online]. [Accessed: 02.11.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-002273-11.

9. Bahlis N, Facon T, Usmani Saad Z et al. Daratumumab Plus Lenalidomide and Dexamethasone (D-Rd) Versus Lenalidomide and Dexamethasone (Rd) in Patients with Newly Diagnosed Multiple Myeloma (NDMM) Ineligible for Transplant: Updated Analysis of Maia. Blood 2019; 134: 1875. https://dx.doi.org/10.1182/blood-2019-123426.

10. Facon T, Kumar S, Plesner T et al. Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma. N Engl J Med 2019; 380(22): 2104-2115. https://dx.doi.org/10.1056/NEJMoa1817249.

11. Facon T, Kumar SK, Plesner T et al. Daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone alone in newly diagnosed multiple myeloma (MAIA): overall survival results from a randomised, open-label, phase 3 trial. The Lancet Oncology 2021; 22(11): 1582-1596. https://dx.doi.org/10.1016/S1470-2045(21)00466-6.

12. Gemeinsamer Bundesausschuss. Nutzenbewertungsverfahren zum Wirkstoff Daratumumab (neues Anwendungsgebiet: Multiples Myelom, neu diagnostiziert, Patienten für autologe Stammzelltransplantation nicht geeignet, Kombination mit Lenalidomid und Dexamethason) [online]. 2020 [Accessed: 04.11.2021]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/521/.

13. Kumar Shaji K, Facon T, Usmani Saad Z et al. Updated Analysis of Daratumumab Plus Lenalidomide and Dexamethasone (D-Rd) Versus Lenalidomide and Dexamethasone (Rd) in Patients with Transplant-Ineligible Newly Diagnosed Multiple Myeloma (NDMM): The Phase 3 Maia Study. Blood 2020; 136: 24-26. https://dx.doi.org/10.1182/blood-2020-134847.

14. Perrot A, Facon T, Plesner T et al. Health-Related Quality of Life in Transplant-Ineligible Patients With Newly Diagnosed Multiple Myeloma: Findings From the Phase III MAIA Trial. J Clin Oncol 2021; 39(3): 227-237. https://dx.doi.org/10.1200/jco.20.01370.

15. Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie. Multiples Myelom: Leitlinie [online]. 2018 [Accessed: 02.11.2021]. URL: https://www.onkopedia.com/de/onkopedia/guidelines/multiples-myelom/@@pdf-latest?filename=multiples-myelom.pdf.

16. Dimopoulos MA, Moreau P, Terpos E et al. Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Ann Oncol 2021; 32(3): 309-322. https://dx.doi.org/10.1016/j.annonc.2020.11.014.

17. Larocca A, Dold SM, Zweegman S et al. Patient-centered practice in elderly myeloma patients: an overview and consensus from the European Myeloma Network (EMN). Leukemia 2018; 32(8): 1697-1712. https://dx.doi.org/10.1038/s41375-018-0142-9.

18. Moreau P, San Miguel J, Sonneveld P et al. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017; 28(Suppl 4): iv52-iv61. https://dx.doi.org/10.1093/annonc/mdx096.

19. European Medicines Agency. Darzalex: extension of indication variation assessment report (CHMP and PRAC Rapporteurs' joint response assessment report and 2nd Request for Supplementary Information); EMA/CHMP/413496/2019 [unpublished]. 2019.

20. Xcenda GmbH. Analyse von neudiagnostizierten Patienten mit Multiplem Myelom anhand von GKV-Routinedaten zur Unterstützung des Modul 3 einer frühen Nutzenbewertung nach § 35a SGB V. Endbericht Version 1.2. 2018.

21. OIS. Oncology Information Service. Projekt: Analyse neu diagnostizierter Patienten mit Multiplem Myelom zur Unterstützung einer frühen Nutzenbewertung nach § 35a SGBV. TherapieMonitor Multiples Myelom. 2018.

22. European Medicines Agency. Darzalex: European public assessment report [online]. 2019 [Accessed: 30.03.2020]. URL: https://www.ema.europa.eu/en/documents/variation-report/darzalex-h-c-4077-ii-0029-epar-assessment-report-variation_en.pdf.

23. Bristol Myers Squibb. Revlimid Hartkapseln [online]. 2021 [Accessed: 10.10.2021]. URL: https://www.fachinfo.de.

24. Janssen. DARZALEX 20 mg/ml Konzentrat zur Herstellung einer Infusionslösung [online]. 2021 [Accessed: 10.10.2021]. URL: https://www.fachinfo.de.

25. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Dokumentation und Würdigung der Anhörung zum Entwurf der Allgemeinen Methoden 6.0 [online]. 2020 [Accessed: 27.01.2021]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_dwa-entwurf-fuer-version-6-0_v1-0.pdf.

26. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Atezolizumab (hepatozelluläres Karzinom) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2021 [Accessed: 01.03.2021]. URL: https://www.iqwig.de/download/a20-97_atezolizumab_nutzenbewertung-35a-sgb-v_v1-0.pdf.

27. Gemeinsamer Bundesausschuss. Antworten auf häufig gestellte Fragen zum Verfahren der Nutzenbewertung; Wie soll, vor dem Hintergrund der Veröffentlichung des Methodenpapiers 6.0 des IQWiG am 5. November 2020, derzeit in der Dossiererstellung mit der Bestimmung von klinischen Relevanzschwellen bei komplexen Skalen umgegangen werden? [online]. [Accessed: 05.08.2021]. URL: https://www.g-ba.de/themen/arzneimittel/arzneimittel-richtlinie-anlagen/nutzenbewertung-35a/faqs.

28. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Isatuximab (multiples Myelom nach ≥ 2 Vortherapien) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2021 [Accessed: 17.08.2021]. URL: https://www.iqwig.de/download/a21-61_isatuximab_nutzenbewertung-35a-sgb-v_v1-0.pdf.

The full report (German version) is published under https://www.iqwig.de/en/projects/a21-126.html.