

Daratumumab (smouldering multiple myeloma)

Benefit assessment according to §35a SGB V¹

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Patient and family involvement

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

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ASCT	autologous stem cell transplant
CTCAE	Common Terminology Criteria for Adverse Events
DGHO	Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (German Society for Haematology and Medical Oncology)
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EHA	European Hematology Association
EMA	European Medicines Agency
EMN	European Myeloma Network
EORTC	European Organisation for Research and Treatment of Cancer
FDA	Food and Drug Administration
FLC	free light chains
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HR	hazard ratio
Ig	immunoglobulin
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PFS	progression-free survival
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-MY20	Quality of Life Questionnaire-Multiple Myeloma 20
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	summary of product characteristics

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug daratumumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the 'company'). The dossier was sent to IQWiG on 18 August 2025.

Research question

The aim of this report is to assess the added benefit of daratumumab compared with watchful waiting as the appropriate comparator therapy (ACT) in adult patients with smouldering multiple myeloma at high risk of developing multiple myeloma.

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

Table 2: Research question for the benefit assessment of daratumumab

Therapeutic indication	ACT ^a
Adult patients with smouldering multiple myeloma who are at high risk of developing multiple myeloma	Watchful waiting
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the specification of the ACT.

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

Study pool and study design

The study pool for this benefit assessment consists of the RCT AQUILA. This concurs with the company's study pool.

AQUILA study

The AQUILA study is an ongoing, open-label RCT comparing daratumumab with no intervention. The study included adults with smouldering multiple myeloma at high risk of developing multiple myeloma. In the study, high risk was defined as $\geq 10\%$ clonal plasma cells in the bone marrow, and ≥ 1 of the following criteria: free light chain (FLC) ratio ≥ 8 to < 100 , serum M-protein ≥ 3 g/dL, clonal plasma cells in the bone marrow $> 50\%$ to $< 60\%$, immunoglobulin (Ig)A subtype, immunoparesis with reduction of 2 uninvolved Ig isotypes.

A total of 390 patients were randomly allocated to the 2 study arms, 194 to the intervention arm and 196 to the comparator arm.

Treatment with daratumumab in the intervention arm was in compliance with the information in the summary of product characteristics (SmPC).

The primary outcome of the AQUILA study was progression-free survival (PFS). Further secondary outcomes were outcomes in the categories of mortality, morbidity, health-related quality of life and side effects.

For the AQUILA study, data from one data cut-off is available to date. This was planned after 165 PFS events and was conducted on 1 May 2024.

The G-BA specified watchful waiting as the ACT. In the AQUILA study, patients in the comparator arm received no intervention, but regular active monitoring of their condition. All enrolled patients received active monitoring visits conducted every 12 weeks until disease progression. The monitoring intervals in the AQUILA study constituted an adequate implementation of the ACT.

Definition of a high risk of developing multiple myeloma in the AQUILA study

In AQUILA, a high risk of developing multiple myeloma was defined as $\geq 10\%$ clonal plasma cells in the bone marrow, and ≥ 1 of the following criteria:

- serum M-protein ≥ 3 g/dL
- clonal plasma cells in the bone marrow $> 50\%$ to $< 60\%$
- FLC ratio ≥ 8 to < 100
- IgA subtype
- immunoparesis with reduction of 2 uninvolved Ig isotypes

This risk classification does not correspond to the current, well-established criteria for smouldering multiple myeloma with a high risk of progression, as developed by the Mayo Clinic (hereinafter referred to as the Mayo risk criteria). According to this more recent risk classification, a high risk of developing multiple myeloma requires ≥ 2 of the following criteria to be met:

- serum M-protein > 2 g/dL
- clonal plasma cells in the bone marrow $> 20\%$
- FLC ratio > 20

The company used the total population of the AQUILA study for the benefit assessment. This approach was appropriate. The European Public Assessment Report published by the European Medicines Agency (EMA) described and discussed the discrepancy between the risk classification in the AQUILA study and the established Mayo risk criteria. As a consequence of the differing risk classification, the EMA explicitly restricted the marketing authorization to those patients who are at high risk according to the inclusion criteria of the pivotal AQUILA study. To this end, Section 4.1 in the German 'Fachinformation' [3] contains a reference to Section 5.1, which sets out the criteria for a high risk of developing multiple myeloma according to the AQUILA study. The total population of the AQUILA study therefore corresponded to the authorized therapeutic indication for daratumumab in smouldering multiple myeloma and was used for the benefit assessment, similar to the company's approach.

Risk of bias

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

For all outcomes relating to morbidity, health-related quality of life and side effects, there was a high risk of bias in the results due to incomplete observations for potentially informative reasons, with differences in follow-up times between the study arms. The open-label study design and subjective recording of outcomes was an additional factor contributing to a high risk of bias in the results of the patient-reported outcomes of symptoms (European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire-Core 30 [QLQ-C30]), health status (EQ-5D visual analogue scale [VAS]), health-related quality of life (EORTC QLQ-C30) and non-severe/non-serious specific AEs. In addition, the outcomes of symptoms (EORTC QLQ-C30), health status (EQ-5D VAS) and health-related quality of life (EORTC-QLQ-C30) were observed under inadequate subsequent therapies, and the follow-up intervals differed between patients with disease progression and those without. These were 2 additional factors contributing to a high risk of bias in the results.

Results

Mortality

Overall survival

The results for the overall survival outcome were not interpretable, as the subsequent antineoplastic therapies administered in the comparator arm of the AQUILA study did not adequately represent the current standard of care following the development of multiple myeloma. Overall, in the comparator arm, only 33.3% of patients receiving first-line treatment for multiple myeloma received a CD38 antibody in this treatment. Across all subsequent lines of treatment, a maximum of 61 (58%) patients in the comparator arm received subsequent therapy with CD38 antibodies.

There is no hint of an added benefit of daratumumab in comparison with watchful waiting; an added benefit is therefore not proven.

Morbidity

Symptoms (EORTC QLQ-C30)

Fatigue, insomnia, constipation and diarrhoea

No statistically significant difference between the study arms was shown for any of the outcomes fatigue, insomnia, constipation and diarrhoea. There is no hint of an added benefit of daratumumab in comparison with watchful waiting; an added benefit is therefore not proven.

Pain and dyspnoea

For the outcomes of pain and dyspnoea, a statistically significant difference in favour of daratumumab was shown in each case. However, the difference was no more than marginal for these outcomes in the category of non-serious/non-severe symptoms/late complications. There is no hint of an added benefit of daratumumab in comparison with watchful waiting; an added benefit is therefore not proven.

Nausea and vomiting

No statistically significant difference between the study arms was shown for the outcome of nausea and vomiting. However, there was an effect modification for the characteristic 'Mayo risk criteria for developing multiple myeloma'. For patients with a high-risk according to the Mayo risk criteria, there is a hint of an added benefit of daratumumab versus watchful waiting. For patients with a low or intermediate risk according to the Mayo risk criteria, there is no hint of an added benefit of daratumumab versus watchful waiting; an added benefit is therefore not proven for patients with a low or intermediate risk according to the Mayo risk criteria with regard to this outcome.

Appetite loss

No statistically significant difference between the study arms was shown for the outcome appetite loss. However, there is an effect modification by the characteristic of age. For patients aged < 65 years, there is a hint of an added benefit of daratumumab versus watchful waiting. For patients aged ≥ 65 years, there is no hint of an added benefit of daratumumab versus watchful waiting; an added benefit is therefore not proven for patients aged ≥ 65 years with regard to this outcome.

Health status (EQ-5D VAS)

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

Health-related quality of life (EORTC QLQ-C30)

Global health status and emotional functioning

A statistically significant difference in favour of daratumumab was shown for each of the outcomes of global health status and emotional functioning. In each case, there is a hint of an added benefit of daratumumab in comparison with watchful waiting.

Physical functioning, role functioning, cognitive functioning, and social functioning

No statistically significant difference between the study arms was shown for any of the following outcomes: physical functioning, role functioning, cognitive functioning and social functioning. In each case, there is no hint of an added benefit of daratumumab in comparison with watchful waiting; an added benefit is therefore not proven.

Side effects

SAEs

For the outcome of SAEs, there is no statistically significant difference between the study arms. There is no hint of greater or lesser harm of daratumumab in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Severe AEs

There is no statistically significant difference between the treatment arms for the outcome of severe AEs. However, there is an effect modification by the characteristic of sex. For men, there is a hint of greater harm of daratumumab in comparison with watchful waiting. For women, there is no hint of greater or lesser harm of daratumumab in comparison with watchful waiting; greater or lesser harm for women is therefore not proven in this outcome.

Discontinuation due to AEs

In AQUILA, discontinuations due to AEs were only recorded only in the intervention arm. No suitable data were therefore available for the outcome of discontinuation due to AEs. There is no hint of greater or lesser harm of daratumumab in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Respiratory, thoracic and mediastinal disorders (System Organ Class [SOC], AEs)

A statistically significant difference to the disadvantage of daratumumab was shown for the outcome of respiratory, thoracic and mediastinal disorders (SOC, AEs). However, there is an effect modification by the characteristic of sex. For women, there is a hint of greater harm of daratumumab in comparison with watchful waiting. For men, there is no hint of greater or lesser harm of daratumumab in comparison with watchful waiting; greater or lesser harm for men is therefore not proven in this outcome.

Specific AEs

A statistically significant difference to the disadvantage of daratumumab was shown for each of the following outcomes: general disorders and administration site conditions (SOC, AEs), gastrointestinal disorders (SOC, AEs), nervous system disorders (SOC, AEs), skin and subcutaneous tissue disorders (SOC, AEs), insomnia (Preferred Term [PT], AEs), vascular disorders (SOC, AEs), ear and labyrinth disorders (SOC, AEs) and infections and infestations (SOC, severe AE). In each case, there is greater harm of daratumumab in comparison with watchful waiting.

A statistically significant difference to the disadvantage of daratumumab was shown for the outcome of respiratory, thoracic and mediastinal disorders (SOC, AEs). However, there is an effect modification by the characteristic of sex. For women, there is a hint of greater harm of daratumumab in comparison with watchful waiting. For men, there is no hint of greater or lesser harm of daratumumab in comparison with watchful waiting; greater or lesser harm for men is therefore not proven in this outcome.

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

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:

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

In terms of positive effects, there is a minor added benefit in the category of health-related quality of life, in the outcomes of global health status and emotional functioning. In addition, there is a minor added benefit for the outcome of nausea and vomiting in patients with a high risk of disease progression according to the Mayo risk criteria, and a considerable added benefit for the outcome of appetite loss in patients aged < 65 years.

On the other hand, there are a multitude of negative effects in the side effects category, which have major and considerable extent. There is greater harm of major extent for the outcome of infections and infestations (severe AEs), and, for men, considerable harm in terms of the overall rate of severe AEs. Furthermore, there are disadvantages of considerable extent of

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].

daratumumab in 8 non-serious/non-severe specific AEs. Overall, many patients in the intervention arm were affected by these AEs. For example, more than twice as many patients in the intervention arm (approx. 60% versus < 30%) had general disorders and administration site conditions and gastrointestinal disorders. Approximately half of the patients in the intervention arm had nervous system disorders (approx. 49% versus 22%).

In summary, there is no hint of an added benefit of daratumumab versus the ACT for adult patients with smouldering multiple myeloma who are at high risk of developing multiple myeloma.

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

Table 3: Daratumumab – probability and extent of added benefit

Therapeutic indication	ACT ^a	Probability and extent of added benefit
Adult patients with smouldering multiple myeloma who are at high risk of developing multiple myeloma	Watchful waiting	Added benefit not proven
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

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

I 2 Research question

The aim of this report is to assess the added benefit of daratumumab compared with watchful waiting as the appropriate comparator therapy (ACT) in adult patients with smouldering multiple myeloma at high risk of developing multiple myeloma.

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

Table 4: Research question for the benefit assessment of daratumumab

Therapeutic indication	ACT ^a
Adult patients with smouldering multiple myeloma who are at high risk of developing multiple myeloma	Watchful waiting
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the specification of the ACT.

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

I 3 Information retrieval and study pool

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

Sources used by the company in the dossier:

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

To check the completeness of the study pool:

- Search of trial registries for studies on daratumumab (last search on 5 September 2025); for search strategies, see I Appendix A of the full dossier assessment

The search did not identify any additional relevant studies.

I 3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: daratumumab vs. watchful waiting

Study	Study category			Available sources		
	Study for the marketing authorization of the drug to be assessed (yes/no)	Sponsored study ^a (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries ^b (yes/no [citation])	Publication (yes/no [citation])
54767414SMM3001 (AQUILA ^c)	Yes	Yes	No	Yes [4]	Yes [5-7]	Yes [8]
a. Study sponsored by the company. b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries. c. In the tables below, the study will be referred to using this acronym. CSR: clinical study report; RCT: randomized controlled trial						

The study pool for this benefit assessment consists of the RCT AQUILA. This concurs with the company's study pool.

I 3.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: daratumumab vs. no intervention

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes ^a
AQUILA	RCT, open-label, parallel	Adults with smouldering multiple myeloma ^b who are at high risk ^c of developing multiple myeloma ▪ ECOG PS ≤ 1	daratumumab (N = 194) No intervention (N = 196)	Screening: ≥ 35 days before randomization Treatment: daratumumab: up to 36 months or 39 cycles or until documented disease progression, unacceptable toxicity or withdrawal of consent, whichever occurs first Observation: outcome-specific ^d , at most until death or end of study ^e	124 centres in Argentina, Australia, Belgium, Brazil, Canada, Czech Republic, Denmark, France, Germany, Greece, Hungary, Israel, Italy, Japan, Netherlands, Norway, Poland, Russia, Spain, Sweden, Turkey, United Kingdom, United States 11/2017–ongoing Data cut-offs: 1 May 2024 ^f	Primary: PFS Secondary: overall survival, morbidity, health-related quality of life, AEs
a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment. b. Defined as serum M-protein ≥ 3 g/dL or urine M-protein ≥ 500 mg/24 hours and/or 10% to 60% clonal plasma cells in the bone marrow, and absence of symptoms of multiple myeloma/amyloidosis. c. High risk defined as ≥ 10% clonal plasma cells in the bone marrow, and ≥ 1 of the following criteria: FLC ratio ≥ 8 to < 100, serum M-protein ≥ 3 g/dL, clonal plasma cells in the bone marrow > 50% to < 60%, IgA subtype, immunoparesis with reduction of 2 uninvolved Ig isotypes (only IgA, IgM and IgG are taken into account). d. Outcome-specific information is provided in Table 10. e. About 8 years after randomization of the last patient. f. Prespecified data cut-off, planned after 165 PFS events. An additional interim analysis planned after 99 PFS events was not conducted. AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FLC: free light chain; IgA: immunoglobulin A; IgG: immunoglobulin G; IgM: immunoglobulin M; N: number of randomized patients; PFS: progression-free survival; RCT: randomized controlled trial						

Table 7: Characteristics of the intervention – RCT, direct comparison: daratumumab vs. no intervention

Study	Intervention	Comparison
AQUILA	Daratumumab 1800 mg, SC ▪ Cycles 1–2: weekly (Days 1, 8, 15 and 22) ▪ Cycles 3–6: every 2 weeks (Days 2 and 15) ▪ Cycles 7–39: every 4 weeks (Day 1) Length of cycle: 28 days Dose modification: ▪ Dose modifications were not permitted; dose delays of up to a maximum of 28 days due to toxicity were possible^a Premedication before daratumumab ▪ 1–3 hours before administration of daratumumab: ▫ paracetamol (650–1000 mg, orally or IV) ▫ antihistamine (25–50 mg diphenhydramine orally or IV, or equivalent) ▫ methylprednisolone (100 mg orally or IV for the first 2 doses, followed by 60 mg^b orally or IV) or equivalent ▪ Recommended in Cycle 1 on Day 1 of the administration of daratumumab: montelukast (10 mg, orally) or equivalent Postmedication after daratumumab ▪ On the 2 days following administration of daratumumab: long- or medium-acting corticosteroid (20 mg methylprednisolone orally or equivalent) ▪ For patients at increased risk of respiratory complications, the following drugs were to be considered following administration of daratumumab: ▫ antihistamines (diphenhydramine or equivalent) on Days 1 and 2 following administration ▫ short-acting beta-2 sympathomimetics (e.g. salbutamol) ▫ control medications for the relevant lung disorder (e.g. inhaled corticosteroids) Allowed concomitant treatment ▪ Any concomitant medications or treatments deemed necessary for supportive care (except disallowed concomitant treatments as listed below) Prohibited prior and concomitant treatment ▪ Other CD38 inhibitors, other monoclonal antibodies or immunomodulators ▪ Systemic corticosteroids (> 10 mg/day of prednisone or equivalent at the time of randomization, or > 280 mg cumulative dose of prednisone or equivalent for any 4-week period in the year prior to study start) ▪ Systemic corticosteroids > 280 mg cumulative dose of prednisone or equivalent for 4 weeks during the study) (except for the treatment of infusion-related reactions) ▪ Other antineoplastic myeloma treatments ▪ Drugs used for other indications that have anti-myeloma properties	No intervention
a. If there is a dose delay of > 28 days, treatment must be discontinued. b. The dose is reduced only if no infusion-related reactions occur after the first 2 doses. IV: intravenous; RCT: randomized controlled trial; SC: subcutaneous		

AQUILA study

The AQUILA study is an ongoing, open-label RCT comparing daratumumab with no intervention. The study included adults with smouldering multiple myeloma at high risk of developing multiple myeloma. In the study, high risk was defined as $\geq 10\%$ clonal plasma cells in the bone marrow, and ≥ 1 of the following criteria: free light chain (FLC) ratio ≥ 8 to < 100 , serum M-protein ≥ 3 g/dL, clonal plasma cells in the bone marrow $> 50\%$ to $< 60\%$, immunoglobulin (Ig)A subtype, immunoparesis with reduction of 2 uninvolved Ig isotypes (see below for details). In addition, the patients' general health at enrolment had to correspond to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of ≤ 1 .

A total of 390 patients were enrolled and randomly allocated in a 1:1 ratio to the 2 study arms (194 to the intervention arm and 196 to the comparator arm). Randomization was stratified by the number of the risk factors for developing multiple myeloma mentioned above (< 3 versus ≥ 3).

Treatment with daratumumab in the intervention arm was in compliance with the information in the summary of product characteristics (SmPC) [3]. See below for details on the implementation of the ACT 'watchful waiting' in the comparator arm.

The primary outcome of the AQUILA study was progression-free survival (PFS). Further secondary outcomes were outcomes in the categories of mortality, morbidity, health-related quality of life and side effects.

For the AQUILA study, data from one data cut-off is available to date. This was planned after 165 PFS events and was conducted on 1 May 2024. The final data cut-off was planned about 8 years after randomization of the last patient. For this benefit assessment, the prespecified data cut (planned after 165 PFS events) from the AQUILA study from 1 May 2024 was used. This concurs with the company's approach.

Implementation of the ACT

The G-BA specified watchful waiting as the ACT. In the AQUILA study, patients in the comparator arm received no intervention, but regular active monitoring of their condition. All enrolled patients received active monitoring visits conducted every 12 weeks until disease progression, in accordance with the SLiM-CRAB criteria [9]. The S3 guideline on the diagnosis, treatment and follow-up of patients with monoclonal gammopathy of undetermined significance (MGUS) or multiple myeloma [10] recommends an annual imaging assessment of the disease over a period of 5 years for patients with smouldering multiple myeloma. For patients with smouldering multiple myeloma and low-intermediate risk of progression, the guideline issued by the European Hematology Association and the European Myeloma Network (EHA/EMN) [11] recommends monitoring intervals of 6 months for patients with a

low risk, and 3 to 6 months for those with an intermediate risk. For patients at high risk of progression, the guideline does not specify the length of the monitoring intervals.

The monitoring intervals in the AQUILA study constituted an adequate implementation of the ACT.

Definition of a high risk of developing multiple myeloma in the AQUILA study

In AQUILA, a high risk of developing multiple myeloma was defined as $\geq 10\%$ clonal plasma cells in the bone marrow, and ≥ 1 of the following criteria:

- serum M-protein ≥ 3 g/dL
- clonal plasma cells in the bone marrow $> 50\%$ to $< 60\%$
- FLC ratio ≥ 8 to < 100
- IgA subtype
- immunoparesis with reduction of 2 uninvolved Ig isotypes

This risk classification does not correspond to the current, well-established criteria for smouldering multiple myeloma with a high risk of progression, as developed by the Mayo Clinic [12] (hereinafter referred to as the Mayo risk criteria). According to this more recent risk classification, a high risk of developing multiple myeloma requires ≥ 2 of the following criteria to be met:

- serum M-protein > 2 g/dL
- clonal plasma cells in the bone marrow $> 20\%$
- FLC ratio > 20

In Module 4 B, the company stated that the Mayo risk criteria only became established after the AQUILA study had begun. It also explained that it had analysed additional results for a high-risk subgroup according to the Mayo risk criteria (40.5% of patients in the total population) and that these were consistent with the results for the total population. It used the total population of the AQUILA study for the benefit assessment.

The company's approach was appropriate. The European Public Assessment Report [13] published by the European Medicines Agency (EMA) described and discussed the discrepancy between the risk classification in the AQUILA study and the established Mayo risk criteria. As a consequence of the differing risk classification, the EMA explicitly restricted the marketing authorization to those patients who are at high risk according to the inclusion criteria of the AQUILA study. To this end, Section 4.1 in the German 'Fachinformation' [3] contains a reference to Section 5.1, which sets out the criteria for a high risk of developing multiple

myeloma according to the AQUILA study. The total population of the AQUILA study therefore corresponded to the authorized therapeutic indication for daratumumab in smouldering multiple myeloma and was used for the benefit assessment, similar to the company's approach. Effect modifications due to the characteristic 'Mayo risk criteria' (low versus intermediate versus high) were investigated as part of this benefit assessment (see Section I 4.4).

It was assumed that, in clinical practice, a high risk of developing multiple myeloma is assessed primarily using the now well-established Mayo risk criteria. However, on-label use of daratumumab requires high risk to be determined based on the inclusion criteria of the AQUILA study. The subgroup analyses presented by the company in accordance with the Mayo risk criteria (approximately 41% of the total population, see also Table 9) showed that a risk assessment based on the inclusion criteria of AQUILA differs from one based on the Mayo criteria for a relevant proportion of patients; consequently, it cannot generally be assumed that the risk assessment is transferable between the 2 definitions. It is possible that patients may be at high risk of developing multiple myeloma according to the Mayo Clinic criteria, but not at high risk according to the criteria of the AQUILA study. Treatment of these patients with daratumumab would not be covered by the marketing authorization. Furthermore, by restricting the marketing authorization to the risk criteria used in the AQUILA study, it would also be possible to treat patients with daratumumab who, according to the now-established Mayo risk criteria, do not present a high risk of progression to multiple myeloma.

I 3.2.1 Planned duration of follow-up

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

Table 8: Planned duration of follow-up observation – RCT, direct comparison: daratumumab vs. no intervention

Study	Planned follow-up
Outcome category	
Outcome	
AQUILA study	
Mortality	
Overall survival	Until death, lost to follow-up, or end of study (whichever occurs first)
Morbidity	
Symptoms (EORTC QLQ-C30)	Until end of study or up to 18 months ^a after disease progression
Health status (EQ-5D VAS)	Until end of study or up to 18 months ^a after disease progression
Health-related quality of life	
EORTC QLQ-C30	Until end of study or up to 18 months ^a after disease progression
Side effects	
All outcomes in the side effects category	▪ Daratumumab arm: 30 days after the last dose of daratumumab or until the start of subsequent treatment, whichever occurs first ▪ Comparator arm: 36 months after study start or until the start of subsequent treatment, whichever occurs first
a. From Amendment 6 of 23 September 2024: up to 6 months after disease progression EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; VAS: visual analogue scale	

It was positively noted that the patient-reported outcomes on morbidity and health-related quality of life were observed well beyond the point of disease progression. However, the observation periods did not cover the entire study period. The observation periods for the outcomes morbidity, health-related quality of life and side effects were systematically shortened, for example. Outcomes in the categories of morbidity and health-related quality of life were recorded up to 18 months after disease progression. Outcomes in the side effects category were recorded only up to 30 days after the last dose of daratumumab in the intervention arm and up to 36 months after the start of the study or the start of subsequent treatment in the comparator arm. However, to draw a reliable conclusion on the total study period or the time to patient death, it would also be necessary to record these outcomes for the total period, as was done for survival.

I 3.2.2 Patient characteristics

Table 9 shows the patient characteristics of the included study.

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: daratumumab vs. no intervention (multipage table)

Study Characteristic Category	daratumumab N = 194	No intervention N = 196
AQUILA		
Age [years], mean (SD)	62 (11)	63 (11)
Sex [F/M], %	51/49	53/47
Family origin, n (%)		
White	161 (83)	162 (83)
Black or African American	4 (2)	7 (4)
Asian	18 (9)	13 (7)
Other ^a	1 (< 1) ^b	5 (3) ^b
Not reported	10 (5)	9 (5)
Disease duration: time from first diagnosis to randomization [months], mean (SD)	14.8 (14.0) ^b	15.1 (15.6) ^b
ECOG PS at baseline, n (%)		
0	165 (85)	160 (82)
1	29 (15)	36 (18)
Myeloma type according to immunofixation or serum FLC measurement, n (%)		
IgG	127 (65)	138 (70)
IgA	55 (28)	42 (21)
Other ^c	12 (6) ^b	16 (8) ^b
Serum M-protein (g/dL), n (%)		
≤ 2	113 (58) ^b	109 (56) ^b
> 2 – < 3	47 (24)	47 (24)
≥ 3	34 (18)	40 (20)
Percentage of plasma cells in the bone marrow (biopsy/aspirate) ^d , n (%)		
< 10	1 (< 1)	0 (0)
≥ 10 – ≤ 20	124 (64)	102 (52)
> 20 – < 40	50 (26)	66 (34)
≥ 40	19 (10)	28 (14)
Serum light chain ratio (involved:uninvolved), n (%)		
< 8	54 (28)	49 (25)
≥ 8 – ≤ 20	53 (27)	63 (32)
> 20	87 (45)	84 (43)
Risk according to Mayo ^e , n (%)		
Low	45 (23)	34 (17)
Intermediate	77 (40)	76 (39)
High	72 (37)	86 (44)

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: daratumumab vs. no intervention (multipage table)

Study Characteristic Category	daratumumab N = 194	No intervention N = 196
Treatment discontinuation, n (%)	66 (34) ^f	— ^g
Study discontinuation, n (%) ^h	30 (15 ^b)	51 (26)
a. This includes Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, and others. b. Institute's calculation; based on the randomized patients. c. Other categories: IgD; kappa type; lambda type; biclonal; serum FLC only. d. The highest proportion of plasma cells in the bone marrow (biopsy/aspirate). e. Mayo risk criteria: serum M-protein > 2 g/dL, ratio of involved to uninvolved free light chains > 20, BMPC > 20%. 0 risk factors = low risk, 1 risk factor = intermediate risk, ≥ 2 risk factors = high risk. f. Common reasons for treatment discontinuation in the intervention arm were the following (percentages based on randomized patients): disease progression (22%), AEs (7%). In addition, 1 of the randomized patients never started treatment. g. Discontinuation of active monitoring: 116 (59%). h. The most common reason for study discontinuation in the intervention vs. the control arm was the following (percentages based on randomized patients): withdrawal of consent (6% vs. 12%). The data additionally include patients who died during the course of the study (intervention arm: 15 [8%] vs. comparator arm: 26 [13%]). AE: adverse event; BMPC: bone marrow plasma cell; ECOG PS: European Cooperative Oncology Group Performance Status; F: female; FLC: free light chain; IgA: immunoglobulin A; IgD: immunoglobulin D; IgG: immunoglobulin G; M: male; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation		

The patient characteristics were largely balanced between the 2 treatment groups of AQUILA. The mean age of the patients was 62 and 63 years, and the majority (83%) were white. The proportion of patients with smouldering multiple myeloma of the IgA subtype was higher in the intervention arm (intervention: 28% versus comparator: 21%), whereas the proportion of patients with the IgG subtype was higher in the comparator arm (intervention: 65% versus comparator: 70%). Based on the Mayo risk criteria, 23% (intervention) versus 17% (comparator) had a low risk, 40% (intervention) versus 39% an intermediate risk, and 37% (intervention) versus 44% (comparator) a high risk of developing multiple myeloma.

I 3.2.3 Course of the study

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

Table 10: Information on the course of the study – RCT, direct comparison: daratumumab vs. no intervention

Study	daratumumab N = 194	No intervention N = 196
Duration of the study phase		
Outcome category/outcome		
AQUILA		
Treatment duration / active monitoring [months]		
Median [min; max]	35.0 [0; 36.1]	25.9 [0.1; 36.0] ^a
Mean (SD)	28.2 (10.9)	24.1 (12.1) ^a
Observation period [months]		
Overall survival ^b		
Median [min; max]	65.9 [7; 76.6]	64.8 [0; 76.4]
Mean (SD)	62.1 (12.0)	56.6 (18.4)
Morbidity (symptoms, health status), health-related quality of life		
EORTC QLQ-C30		
Median [min; max]	50.8 [ND]	37.4 [ND]
Mean (SD)	[ND]	[ND]
EQ-5D VAS		
Median [min; max]	51.1 [ND]	38.0 [N D]
Mean (SD)	[ND]	[ND]
Side effects		
Median [min; max]	35.9 [ND]	26.8 [ND]
Mean (SD)	[ND]	[ND]
a. This information refers to the observation period until disease progression.		
b. Calculated using the inverse Kaplan-Meier method.		
EORTC: European Organisation for Research and Treatment of Cancer; max: maximum; min: minimum; N: number of patients; ND: no data; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale		

The median treatment duration in the AQUILA study was notably longer in the intervention arm (approx. 35 months) than the corresponding observation period in the comparator arm (approx. 26 months).

The median observation period for the outcome of overall survival was comparable between the study arms (66 versus 65 months). The median observation periods for the outcomes in the categories morbidity, health-related quality of life and side effects were around 25% longer in the intervention arm than in the comparator arm.

I 3.2.4 Subsequent therapies

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

Table 11: Information on subsequent antineoplastic therapies (≥ 2 patients in ≥ 1 treatment arm) – RCT, direct comparison: daratumumab vs. no intervention (multipage table)

Study Treatment regimen ^a	Patients with subsequent therapy, n (%)	
	daratumumab N = 194	No intervention N = 196
AQUILA		
1st subsequent therapy – total population		
Total	64 (33.0)	105 (53.6)
CD38 antibodies ^c total	16 (25.0 ^b)	35 (33.3 ^b)
1st subsequent therapy – ASCT suitable		
Total	23 (11.9)	41 (20.9)
bortezomib-dexamethasone-lenalidomide-melphalan	8 (34.8 ^b)	15 (36.6 ^b)
bortezomib-dexamethasone-lenalidomide-melphalan-thalidomide	3 (13.0 ^b)	6 (14.6 ^b)
bortezomib-carfilzomib-dexamethasone-isatuximab-lenalidomide-melphalan	2 (8.7 ^b)	0 (0 ^b)
bortezomib-cyclophosphamide-dexamethasone-lenalidomide-melphalan	1 (4.3 ^b)	5 (12.2 ^b)
bortezomib-daratumumab-dexamethasone-lenalidomide-melphalan	1 (4.3 ^b)	4 (9.8 ^b)
CD38 antibodies ^c total	4 (17.4 ^b)	7 (17.1 ^b)
2nd subsequent therapy – ASCT suitable^d		
Total	1 (0.5)	4 (2.0)
1st subsequent therapy – ASCT unsuitable		
Total	41 (21.1)	64 (32.7)
bortezomib-dexamethasone-lenalidomide	8 (19.5 ^b)	9 (14.1 ^b)
dexamethasone-lenalidomide	5 (12.2 ^b)	7 (10.9 ^b)
bortezomib-cyclophosphamide-dexamethasone	4 (9.8 ^b)	9 (14.1 ^b)
bortezomib-dexamethasone-thalidomide	4 (9.8 ^b)	1 (1.6 ^b)
daratumumab-dexamethasone-lenalidomide	4 (9.8 ^b)	10 (15.6 ^b)
bortezomib-daratumumab-dexamethasone-lenalidomide	2 (4.9 ^b)	4 (6.3 ^b)
bortezomib-dexamethasone	2 (4.9 ^b)	1 (1.6 ^b)
daratumumab	2 (4.9 ^b) ^e	0 (0 ^b)
carfilzomib-dexamethasone-lenalidomide	1 (2.4 ^b)	2 (3.1 ^b)
bortezomib-daratumumab-dexamethasone-lenalidomide-melphalan-prednisone	0 (0 ^b)	2 (3.1 ^b)
bortezomib-daratumumab-melphalan-prednisone	0 (0 ^b)	3 (4.7 ^b)
bortezomib-dexamethasone-isatuximab-lenalidomide	0 (0 ^b)	3 (4.7 ^b)
CD38 antibodies ^c total	12 (29.3 ^b)	28 (43.8 ^b)

Table 11: Information on subsequent antineoplastic therapies (≥ 2 patients in ≥ 1 treatment arm) – RCT, direct comparison: daratumumab vs. no intervention (multipage table)

Study Treatment regimen ^a	Patients with subsequent therapy, n (%)	
	daratumumab N = 194	No intervention N = 196
2nd subsequent therapy – ASCT unsuitable		
Total	17 (8.8)	29 (14.8)
dexamethasone-lenalidomide	4 (23.5 ^b)	2 (6.9 ^b)
daratumumab-dexamethasone-lenalidomide	0 (0 ^b)	5 (17.2 ^b)
bortezomib-daratumumab-dexamethasone-lenalidomide	0 (0 ^b)	2 (6.9 ^b)
bortezomib-daratumumab-dexamethasone	0 (0 ^b)	8 (27.6 ^b)
dexamethasone-ixazomib-lenalidomide	2 (11.8 ^b)	0 (0 ^b)
CD38 antibodies ^c total	3 (17.6 ^b)	18 (62.1 ^b)
a. All drugs assigned to the respective line of treatment. In some cases, the drugs in the line of treatment were administered sequentially. b. Institute's calculation based on the proportion of patients with subsequent therapy. c. Daratumumab or isatuximab. d. None of the 2nd subsequent therapies used in this patient group met the predefined thresholds for presentation (≥ 2 patients in ≥ 1 treatment arm). e. Daratumumab monotherapy was continued. ASCT: autologous stem cell transplantation; n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial		

The guideline recommendations for multiple myeloma are the key reference for the assessment of the subsequent therapies administered in the comparator arm of AQUILA. According to the 2025 EHA/EMN recommendations [11], first-line treatment for multiple myeloma should include a CD38 antibody (daratumumab or isatuximab), regardless of eligibility for autologous stem cell transplantation (ASCT). These recommendations are largely in line with those issued by the German Society for Haematology and Medical Oncology (DGHO) in 2024 [14].

In the AQUILA study, there were no restrictions regarding subsequent therapy following the development of multiple myeloma. At the first data cut-off, 62 (32.0%) patients in the intervention arm and 100 (51.0%) patients in the comparator arm had developed multiple myeloma. 64 (33.0%) of the patients in the intervention arm and 105 (53.6%) in the comparator arm received at least one subsequent therapy (see Table 11). It was therefore assumed that all patients diagnosed with multiple myeloma during the course of the study received subsequent therapy.

Subsequent therapies in the comparator arm

According to the recommendations set out in the EHA/EMN guideline for patients who are eligible for ASCT, quadruple combination therapies incorporating a CD38 antibody (daratumumab or isatuximab) are the preferred option for induction therapy before ASCT. For patients who are ineligible for ASCT, triple and quadruple combination therapies using CD38 antibodies are described as the preferred option. In AQUILA, 7 out of 41 (17.1%) patients in the comparator arm who were eligible for ASCT received subsequent therapy with a CD38 antibody. 28 out of 64 (43.8%) patients in the comparator arm who were ineligible for ASCT were treated with a CD38 antibody as part of their first subsequent therapy. Overall, in the comparator arm, only 33.3% of patients receiving first-line treatment for multiple myeloma were thus treated with a CD38 antibody in accordance with the recommendations.

The company also provided details on all other lines of subsequent antineoplastic therapies, showing that, in later lines of treatment, a further 26 patients in the comparator arm were treated with CD38 antibodies (18 [ASCT unsuitable] and 2 [ASCT suitable] in the second line of treatment, and 6 in the third or later line of treatment). Together with the data on first-line treatment, this resulted in a maximum total of 61 (58%) patients who received subsequent therapy with CD38 antibodies, regardless of the line of treatment.

Subsequent therapies in the intervention arm

As, in accordance with the guideline, smouldering multiple myeloma is currently only monitored, but not treated, there are no recommendations for subsequent therapy following the development of multiple myeloma whilst on daratumumab monotherapy. A large proportion of patients in the intervention arm received triple and quadruple combination therapies as subsequent therapies. The most common first-line treatments for patients eligible for ASCT were bortezomib-dexamethasone-lenalidomide-melphalan (34.8%) and bortezomib-dexamethasone-lenalidomide-melphalan-thalidomide (13.0%). Patients in the intervention arm for whom ASCT was not an option were most commonly treated with bortezomib-dexamethasone-lenalidomide (19.5%) and dexamethasone-lenalidomide (12.2%) as first-line therapy. A total of 16 out of 64 (25%) patients received first-line treatment with a CD38 antibody, despite having already been treated for smouldering multiple myeloma with daratumumab.

Assessment of the subsequent therapies used

For a large proportion of patients in the comparator arm who developed multiple myeloma during the course of the study, the treatment they received did not comply with the recommendations for the treatment of multiple myeloma. Given the clear recommendations for the use of CD38 antibodies in the first-line treatment of multiple myeloma, as well as several G-BA resolutions confirming an added benefit, it was assumed that further patients in the comparator arm would have benefited from subsequent therapy with CD38 antibodies

[11,14-17]. This was also criticized in a response to the publication of the study results [18]. One particular point of criticism is that the timing of the AQUILA study would have allowed for protocol amendments to enable the use of appropriate subsequent therapies. Although recruitment for the AQUILA study began in November 2017, marketing authorization for daratumumab in combination with bortezomib, melphalan and prednisone for patients who are ineligible for ASCT was granted by the Food and Drug Administration (FDA) in May 2018, and by the European Commission in August 2018. Approximately 1 year after the start of the AQUILA study, the G-BA had already determined a considerable added benefit for daratumumab in combination with bortezomib, melphalan and prednisone for patients for whom ASCT is not suitable [19]. At this early stage of the AQUILA study, only a small number of patients had been diagnosed with multiple myeloma; these patients could therefore have benefited from the inclusion of daratumumab-based combination therapies as subsequent therapy in the study protocol. The deficiencies in subsequent therapies were assessed as substantial and therefore affected the interpretability of the overall survival outcome (see Section I 4.3). Furthermore, the deficiencies regarding the subsequent therapies were taken into account in the assessment of the outcome-specific risk of bias for symptoms (recorded using the European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire-Core 30 [QLQ-C30]), health status (recorded using the visual analogue scale [VAS] of the EQ-5D) and health-related quality of life (recorded using the EORTC QLQ-C30) (see Section I 4.2).

I 3.2.5 Risk of bias across outcomes (study level)

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

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: daratumumab vs. no intervention

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

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

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

I 3.2.6 Transferability of the study results to the German health care context

The company generally considered the findings of the AQUILA study to be transferable to the German health care context. It justified this by pointing out that one-quarter of the study participants were from Western Europe or the United States, and that just under 80% of the study participants were of white family origin. It added that the AQUILA study showed no signs of biodynamic or kinetic differences between the individual population groups or countries involved versus Germany to the extent that they would have a substantial impact on the study results.

In accordance with the criteria set out in the study protocol, the AQUILA study included adults with smouldering multiple myeloma who were at high risk of developing multiple myeloma, the company explained, and this study population also formed the basis for the marketing authorization in this therapeutic indication in the daratumumab SmPC. Following the start of AQUILA in 2017, the Mayo risk criteria for the definition of patients with smouldering multiple myeloma who are at high risk of developing multiple myeloma became increasingly established in the literature, the company added, which is why additional results for the Mayo risk criteria subgroup were analysed for the AQUILA study. According to the company, these findings were consistent with those for the total population in the AQUILA study, and accordingly, the findings of the AQUILA study were also transferable to the German health care context with regard to the definition of high risk.

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

I 4 Results on added benefit

I 4.1 Outcomes included

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

- Mortality
 - Overall survival
- Morbidity
 - Symptoms, recorded with the EORTC QLQ-C30
 - Health status, recorded with the EQ-5D VAS
- Health-related quality of life
 - recorded with the EORTC QLQ-C30
- Side effects
 - Serious adverse events (SAEs)
 - Severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
 - Discontinuation due to AEs
 - Other specific AEs, if any

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

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

Table 13: Matrix of outcomes – RCT, direct comparison: daratumumab vs. no intervention

Study	Outcomes							
	Overall survival	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs ^a	Discontinuation due to AEs	Specific AEs ^b
AQUILA	No ^c	Yes	Yes	Yes	Yes	Yes	No ^d	Yes
a. Severe AEs are operationalized as CTCAE grade ≥ 3. b. The following events were considered (coded according to MedDRA): general disorders and administration site conditions (SOC, AEs), gastrointestinal disorders (SOC, AEs), nervous system disorders (SOC, AEs), respiratory, thoracic and mediastinal disorders (SOC, AEs), skin and subcutaneous tissue disorders (SOC, AEs), insomnia (PT, AEs), vascular disorders (SOC, AEs), ear and labyrinth disorders (SOC, AEs), infections and infestations (SOC, severe AEs). c. Data not interpretable due to inadequate subsequent therapy; see Sections I 3.2.4 and I 4.1 for reasons. d. No suitable data available; see body of text below for reasons. AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale								

Results on overall survival not interpretable due to inadequate subsequent therapies

An observed effect in the outcome of overall survival is not only influenced by the initial study treatment, but also by the subsequent antineoplastic therapies used after disease progression. A meaningful interpretation of an observed effect in the outcome of overall survival therefore requires an appropriate, guideline-compliant subsequent treatment of patients after disease progression. As described in Section I 3.2.4, the deficiencies in the administration of subsequent therapies were assessed as serious.

Although the observed effect in the overall survival outcome was statistically significant (hazard ratio [HR]: 0.52; 95% confidence interval: [0.27; 0.98]; see I Appendix D of the full dossier assessment), the upper limit of the confidence interval indicated that the effect was only to a small extent. Given the inadequate subsequent therapies in the comparator arm, it remained unclear whether there actually was an advantage of daratumumab in the overall survival outcome. The results for the overall survival outcome were therefore assessed as uninterpretable and were not used for the benefit assessment.

Analyses of patient-reported outcomes on morbidity and health-related quality of life

In Module 4 B, the company provided responder analyses for the EORTC QLQ-C30 regarding the time to first deterioration/improvement, and the time to first confirmed improvement/deterioration of ≥ 10 points and $\geq 15\%$ of the scale range (scale range 0 to 100 in each case). Due to the expected progressive course of the disease in the given therapeutic indication, an analysis of the deterioration in symptoms and health-related quality of life was primarily relevant for this benefit assessment. For the benefit assessment procedure, only analyses for the response criterion of 10 points are to be presented in the dossier for EORTC questionnaires [20]. These were used for the benefit assessment.

In AQUILA, patient-reported outcomes were recorded during treatment or active monitoring at screening, Week 12, Week 24 and Week 60, then once a year, and at the end of treatment or the end of active monitoring. For patients without disease progression, annual recordings were carried out as part of the follow-up until the end of the study. Following disease progression, the patient-reported outcomes were recorded at the time of disease progression and subsequently at Months 3, 6, 12 and 18 after disease progression. From Amendment 6 of 23 September 2024 onwards, recording took place only at the time of disease progression, and subsequently at Months 3 and 6 after disease progression. The recording interval for patient-reported outcomes therefore depended on the parameter of disease progression. More frequent recordings following disease progression increase the likelihood of observing changes (e.g. in symptoms) in patients with disease progression versus patients without disease progression. In the case of a potentially simultaneous change in patient-reported outcomes in the treatment arms, this may result in such a change being detected at an earlier stage in the treatment arm where disease progression occurs sooner. The probability of observing a change is therefore higher in the treatment arm with earlier progression events (in this case, the comparator arm). However, given the available data, it can be inferred from the Kaplan-Meier curves that the different recording intervals based on the progression events were not decisive for the observed effects (see I Appendix C of the full dossier assessment). It was therefore possible to use the analyses of the time to first deterioration for the benefit assessment, but this aspect was taken into account in the outcome-specific risk of bias.

The analyses of the time to first deterioration and the time to confirmed deterioration were carried out post hoc for the present dossier. The analyses of the time to confirmed deterioration lacked details on the precise operationalization. For example, it was unclear in how many subsequent recordings the threshold needed to be exceeded to be classified as an event. The time to first deterioration of ≥ 10 points was therefore used for this benefit assessment. For the health status outcome, recorded using the EQ-5D VAS, the time to the first deterioration of ≥ 15 points was used.

EORTC Quality of Life Questionnaire-Multiple Myeloma Module 20 (QLQ-MY20)

In Module 4 B, the company presented the results of the EORTC QLQ-MY20 in addition to those of the EORTC QLQ-C30. The EORTC QLQ-MY20 comprises the symptom scales 'disease symptoms' and 'side effects of treatment', and the functional scales 'future perspective' and 'body image'. However, of these 4 scales, only the 'disease symptoms' and 'future perspective' scales were recorded in the AQUILA study. The company did not provide any justification for the selective recording of the EORTC QLQ-MY20 scales, nor did it provide any information on the validity of the individual scales. This approach was not appropriate. In order to interpret the results of the EORTC QLQ-MY20 appropriately, the questionnaire must be recorded in full. The 2 selectively recorded scales – 'disease symptoms' and 'future perspective' – from the EORTC QLQ-MY20 were not used for the benefit assessment.

Discontinuation due to AEs

In AQUILA, discontinuations due to AEs were only recorded only in the intervention arm. As no intervention was administered in the comparator arm, treatment discontinuation was not possible in this arm. No suitable data were available for this benefit assessment for the outcome of discontinuation due to AEs.

I 4.2 Risk of bias

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

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: daratumumab vs. no intervention

Study	Study level	Outcomes							
		Overall survival	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs ^a	Discontinuation due to AEs	Specific AEs ^b
AQUILA	L	.. ^c	H ^d , e, f, g	H ^d , e, f, g	H ^d , e, f, g	H ^e	H ^e	.. ^h	H ^e , i

a. Severe AEs are operationalized as CTCAE grade ≥ 3 .
b. The following events were considered (coded according to MedDRA): general disorders and administration site conditions (SOC, AEs), gastrointestinal disorders (SOC, AEs), nervous system disorders (SOC, AEs), respiratory, thoracic and mediastinal disorders (SOC, AEs), skin and subcutaneous tissue disorders (SOC, AEs), insomnia (PT, AEs), vascular disorders (SOC, AEs), ear and labyrinth disorders (SOC, AEs), infections and infestations (SOC, severe AEs).
c. Data not interpretable due to inadequate subsequent therapy; see Sections I 3.2.4 and I 4.1 for reasons.
d. Lack of blinding in subjective recording of outcomes.
e. Incomplete observations for potentially informative reasons because of differing follow-ups.
f. Due to uncertainties in the use of adequate subsequent therapies.
g. Different follow-up intervals for patients with disease progression versus those without disease progression; see Section I 4.1.
h. No suitable data available; see Section I 4.1 for the reasoning.
i. For non-severe/non-serious AEs, lack of blinding in subjective recording of outcomes.
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

No suitable data were available for the outcome of overall survival and discontinuation due to AEs (see Sections I 3.2.4 and I 4.1).

For all outcomes relating to morbidity, health-related quality of life and side effects, there was a high risk of bias in the results due to incomplete observations for potentially informative reasons, with differences in follow-up times between the study arms. The open-label study design and subjective recording of outcomes was an additional factor contributing to a high risk of bias in the results of the patient-reported outcomes of symptoms (EORTC QLQ-C30), health status (EQ-5D VAS), health-related quality of life (EORTC QLQ-C30) and non-severe/non-serious specific AEs. In addition, the outcomes of symptoms (EORTC QLQ-C30), health status (EQ-5D VAS) and health-related quality of life (EORTC-QLQ-C30) were observed under inadequate subsequent therapies (see Section I 3.2.4), and the follow-up intervals

differed between patients with disease progression and those without (see Section I 4.1). These were 2 additional factors contributing to a high risk of bias in the results.

I 4.3 Results

Table 15 summarizes the results of the comparison of daratumumab with no intervention in adult patients with smouldering multiple myeloma who are at high risk of developing multiple myeloma. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

The Kaplan-Meier curves on the time-to-event analyses are presented in I Appendix C of the full dossier assessment, and the tables on common AEs, SAEs and severe AEs in I Appendix B of the full dossier assessment. The results on overall survival presented by the company are shown as supplementary information in I Appendix D of the full dossier assessment.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: daratumumab vs. no intervention (multipage table)

Study	daratumumab		No intervention		daratumumab vs. no intervention
Outcome category					
Outcome	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
AQUILA					
Mortality					
Overall survival	No suitable data ^b				
Morbidity					
Symptoms (EORTC QLQ-C30 – time to first deterioration ^c)					
Fatigue	194	10.22 [5.72; 14.32] 128 (66.0)	196	13.73 [6.64; 14.06] 126 (64.3)	0.88 [0.69; 1.13]; 0.321
Nausea and vomiting	194	68.24 [61.57; NC] 65 (33.5)	196	67.68 [51.28; NC] 65 (33.2)	0.78 [0.55; 1.11]; 0.169
Pain	194	25.23 [14.13; 35.98] 116 (59.8)	196	14.72 [11.17; 27.63] 118 (60.2)	0.73 [0.57; 0.95]; 0.020
Dyspnoea	194	60.72 [41.40; NC] 83 (42.8)	196	31.11 [24.64; 63.08] 88 (44.9)	0.71 [0.53; 0.97]; 0.031
Insomnia	194	35.48 [19.75; 52.47] 104 (53.6)	196	26.51 [18.04; 47.47] 93 (47.4)	0.91 [0.69; 1.21]; 0.509
Appetite loss	194	67.71 [60.62; NC] 71 (36.6)	196	57, 95 [33.25; 67.68] 74 (37.8)	0.78 [0.56; 1.08]; 0.142
Constipation	194	63.77 [49.41; 67.71] 82 (42.3)	196	49.51 [41.43; 58.02] 77 (39.3)	0.85 [0.62; 1.16]; 0.309
Diarrhoea	194	NA [48.13; NC] 75 (38.7)	196	50.63 [36.01; NC] 71 (36.2)	0.94 [0.68; 1.31]; 0.723
Health status (time to first deterioration ^d)					
EQ-5D VAS	194	60.85 [49.84; NC] 80 (41.2)	196	55.20 [33.58; NC] 79 (40.3)	0.83 [0.61; 1.14]; 0.256
Health-related quality of life					
EORTC QLQ-C30 (time to first deterioration ^e)					
Global health status	194	29.37 [14.32; 48.13] 108 (55.7)	196	18.96 [10.94; 26.18] 111 (56.6)	0.76 [0.58; 0.99]; 0.045
Physical functioning	194	41.76 [29.18; 60.62] 103 (53.1)	196	30.69 [18.07; 46.39] 97 (49.5)	0.83 [0.63; 1.10]; 0.190

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: daratumumab vs. no intervention (multipage table)

Study Outcome category Outcome	daratumumab		No intervention		daratumumab vs. no intervention
	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
Role functioning	194	19.25 [13.96; 25.86] 115 (59.3)	196	20.47 [13.80; 31.44] 110 (56.1)	0.89 [0.68; 1.15]; 0.365
Emotional functioning	194	53.95 [36.27; 61.70] 91 (46.9)	196	29.77 [23.85; 49.71] 95 (48.5)	0.69 [0.51; 0.92]; 0.012
Cognitive functioning	194	50.76 [28.16; 64.23] 92 (47.4)	196	28.09 [17.15; 47.47] 97 (49.5)	0.77 [0.57; 1.02]; 0.070
Social functioning	194	49.81 [25.04; 62.00] 94 (48.5)	196	38.80 [30.82; 50.63] 92 (46.9)	0.87 [0.65; 1.16]; 0.338
Side effects					
AEs (supplementary information)	193	0.13 [0.07; 0.26] 187 (96.9)	196	3.68 [2.89; 5.06] 162 (82.7)	–
SAEs	193	NA [36.93; NC] 56 (29.0)	196	NA 38 (19.4)	1.47 [0.97; 2.22]; 0.071
Severe AEs ^f	193	36.93 [35.74; NC] 78 (40.4)	196	NA 60 (30.6)	1.33 [0.94; 1.86]; 0.102
Discontinuation due to AEs			No suitable data ^g		
General disorders and administration site conditions (SOC, AEs)	193	4.96 [2.37; 10.68] 126 (65.3)	196	NA 57 (29.1)	3.40 [2.48; 4.67]; < 0.001
Gastrointestinal disorders (SOC, AEs)	193	10.88 [7.10; 14.82] 119 (61.7)	196	NA 52 (26.5)	3.10 [2.23; 4.29]; < 0.001
Nervous system disorders (SOC, AEs)	193	32.89 [13.31; NC] 94 (48.7)	196	NA 43 (21.9)	2.73 [1.90; 3.92]; < 0.001
Respiratory, thoracic and mediastinal disorders (SOC, AEs)	193	NA [20.47; NC] 85 (44.0)	196	NA 41 (20.9)	2.52 [1.73; 3.66]; < 0.001
Skin and subcutaneous tissue disorders (SOC, AEs)	193	NA [36.47; NC] 77 (39.9)	196	NA 20 (10.2)	4.48 [2.73; 7.33]; < 0.001
Insomnia (PT, AEs)	193	NA 43 (22.3)	196	NA 5 (2.6)	9.48 [3.75; 23.97]; < 0.001
Vascular disorders (SOC, AEs)	193	NA 51 (26.4)	196	NA 23 (11.7)	2.35 [1.43; 3.85]; < 0.001

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: daratumumab vs. no intervention (multipage table)

Study Outcome category Outcome	daratumumab		No intervention		daratumumab vs. no intervention
	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
Ear and labyrinth disorders (SOC, AEs)	193	NA 21 (10.9)	196	NA 6 (3.1)	3.61 [1.46; 8.95]; 0.006
Infections and infestations (SOC, severe AEs)	193	NA [36.93; NC] 32 (16.6)	196	NA 9 (4.6)	3.71 [1.74; 7.93]; < 0.001

a. Cox proportional hazards model with treatment as the sole explanatory variable, and with the stratification factor of the number of risk factors associated with progression to multiple myeloma (< 3 risk factors vs. ≥ 3 risk factors).
b. See Section I 4.1 for reasons.
c. A score increase by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range 0 to 100).
d. A score decrease of ≥ 15 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
e. A score decrease of ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
f. Operationalized as CTCAE grade ≥ 3.
g. AEs leading to treatment discontinuation are recorded only in the intervention arm. In the intervention arm, 11 (5.7%) patients discontinued treatment due to AEs.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

On the basis of the available information, no more than hints, e.g. of an added benefit, can be determined for all outcomes.

Mortality

No suitable data were available for the outcome of overall survival (see Section I 4.1). There is no hint of an added benefit of daratumumab in comparison with watchful waiting; an added benefit is therefore not proven.

Morbidity

Symptoms (EORTC QLQ-C30)

Fatigue, insomnia, constipation and diarrhoea

No statistically significant difference between the study arms was shown for any of the outcomes fatigue, insomnia, constipation and diarrhoea. There is no hint of an added benefit of daratumumab in comparison with watchful waiting; an added benefit is therefore not proven.

Pain and dyspnoea

For the outcomes of pain and dyspnoea, a statistically significant difference in favour of daratumumab was shown in each case. However, the difference was no more than marginal for these outcomes in the category of non-serious/non-severe symptoms/late complications. There is no hint of an added benefit of daratumumab in comparison with watchful waiting; an added benefit is therefore not proven.

Nausea and vomiting

No statistically significant difference between the study arms was shown for the outcome of nausea and vomiting. However, there was an effect modification for the characteristic 'risk for developing multiple myeloma according to the Mayo criteria' (see Table 16). For patients with a high-risk according to the Mayo risk criteria, there is a hint of an added benefit of daratumumab versus watchful waiting. For patients with a low or intermediate risk according to the Mayo risk criteria, there is no hint of an added benefit of daratumumab versus watchful waiting; an added benefit is therefore not proven for patients with a low or intermediate risk according to the Mayo risk criteria with regard to this outcome.

Appetite loss

No statistically significant difference between the study arms was shown for the outcome appetite loss. There was an effect modification by the characteristic of age, however (see Table 16). For patients aged < 65 years, there is a hint of an added benefit of daratumumab versus watchful waiting. For patients aged ≥ 65 years, there is no hint of an added benefit of daratumumab versus watchful waiting; an added benefit is therefore not proven for patients aged ≥ 65 years with regard to this outcome.

Health status (EQ-5D VAS)

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

Health-related quality of life (EORTC QLQ-C30)

Global health status and emotional functioning

A statistically significant difference in favour of daratumumab was shown for each of the outcomes of global health status and emotional functioning. In each case, there is a hint of an added benefit of daratumumab in comparison with watchful waiting.

Physical functioning, role functioning, cognitive functioning, and social functioning

No statistically significant difference between the study arms was shown for any of the following outcomes: physical functioning, role functioning, cognitive functioning and social functioning. In each case, there is no hint of an added benefit of daratumumab in comparison with watchful waiting; an added benefit is therefore not proven.

Side effects

SAEs

For the outcome of SAEs, there is no statistically significant difference between the study arms. There is no hint of greater or lesser harm of daratumumab in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Severe AEs

There is no statistically significant difference between the treatment arms for the outcome of severe AEs. There was an effect modification by the characteristic of sex, however (see Table 16). For men, there is a hint of greater harm of daratumumab in comparison with watchful waiting. For women, there is no hint of greater or lesser harm of daratumumab in comparison with watchful waiting; greater or lesser harm for women is therefore not proven in this outcome.

Discontinuation due to AEs

No suitable data were available for the outcome of discontinuation due to AEs (see Section I 4.1). There is no hint of greater or lesser harm of daratumumab in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Specific AEs

A statistically significant difference to the disadvantage of daratumumab was shown for each of the following outcomes: general disorders and administration site conditions (SOC, AEs), gastrointestinal disorders (SOC, AEs), nervous system disorders (SOC, AEs), skin and subcutaneous tissue disorders (SOC, AEs), insomnia (Preferred Term [PT], AEs), vascular disorders (SOC, AEs), ear and labyrinth disorders (SOC, AEs) and infections and infestations (SOC, severe AE). In each case, there is greater harm of daratumumab in comparison with watchful waiting.

A statistically significant difference to the disadvantage of daratumumab was shown for the outcome of respiratory, thoracic and mediastinal disorders (SOC, AEs). There was an effect modification by the characteristic of sex, however (see Table 16). For women, there is a hint of greater harm of daratumumab in comparison with watchful waiting. For men, there is no hint of greater or lesser harm of daratumumab in comparison with watchful waiting; greater or lesser harm for men is therefore not proven in this outcome.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics were taken into account for this benefit assessment:

- Age (< 65 years versus ≥ 65 years)
- Sex (male versus female)
- Risk for developing multiple myeloma according to the Mayo criteria (low vs. intermediate vs. high)

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

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

The results are presented in Table 16. The Kaplan-Meier curves on the subgroup results are presented in I Appendix C.4 of the full dossier assessment.

Table 16: Subgroups (morbidity, side effects) – RCT, direct comparison: daratumumab vs. no intervention (multipage table)

Study Outcome Characteristic Subgroup	daratumumab		No intervention		daratumumab vs. no intervention	
	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] ^a	p-value ^a
AQUILA						
Nausea and vomiting (EORTC QLQ-C30 – time to first deterioration^b)						
Risk according to Mayo criteria						
Low	45	NA [26.38; NC] 17 (37.8)	34	NA 5 (14.7)	2.63 [0.97; 7.15]	0.058
Intermediate	77	68.24 [50.17; NC] 25 (32.5)	76	67.68 [51.28; NC] 25 (32.9)	0.88 [0.51; 1.54]	0.666
High	72	67.71 [49.41; NC] 23 (31.9)	86	33.15 [19.78; NC] 35 (40.7)	0.47 [0.28; 0.81]	0.007
Total					Interaction ^c :	0.026
Appetite loss (EORTC QLQ-C30 – time to first deterioration^b)						
Age						
< 65 years	106	NA [61.57; NC] 28 (26.4)	98	49.71 [24.87; NC] 39 (39.8)	0.45 [0.27; 0.73]	0.001
≥ 65 years	88	36.24 [19.88; NC] 43 (48.9)	98	60.68 [33.25; NC] 35 (35.7)	1.37 [0.88; 2.15]	0.164
Total					Interaction ^c :	< 0.001
Severe AEs^d						
Sex						
Male	95	30.16 [13.93; NC] 49 (51.6)	93	NA [33.08; NC] 28 (30.1)	1.93 [1.21; 3.08]	0.006
Female	98	NA 29 (29.6)	103	NA 32 (31.1)	0.87 [0.53; 1.44]	0.592
Total					Interaction ^c :	0.022
Respiratory, thoracic and mediastinal disorders (SOC, AEs)						
Sex						
Male	95	NA [21.26; NC] 36 (37.9)	93	NA 24 (25.8)	1.62 [0.96; 2.72]	0.069
Female	98	23.06 [7.03; NC] 49 (50.0)	103	NA 17 (16.5)	3.89 [2.23; 6.78]	< 0.001
Total					Interaction ^c :	0.026

Table 16: Subgroups (morbidity, side effects) – RCT, direct comparison: daratumumab vs. no intervention (multipage table)

Study Outcome	daratumumab		No intervention		daratumumab vs. no intervention	
	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] ^a	p-value ^a
a. Calculated using the Cox proportional hazards model, with treatment as the sole explanatory variable and no stratification factor. b. A score increase of ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range 0 to 100). c. p-value for the interaction term calculated using an unstratified Cox proportional hazards model with a treatment $\times$ subgroup characteristic interaction term. d. Operationalized as CTCAE grade ≥ 3. AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class						

Morbidity

Nausea and vomiting

For the outcome of nausea and vomiting, there is a statistically significant effect modification by the characteristic ‘risk for developing multiple myeloma according to the Mayo criteria’. For patients with a high-risk according to the Mayo risk criteria, there was a statistically significant difference in favour of daratumumab versus watchful waiting. For patients with a high-risk according to the Mayo risk criteria, there is a hint of an added benefit of daratumumab versus watchful waiting. For patients with a low or intermediate risk according to the Mayo risk criteria, however, there was no statistically significant difference between the study arms. For these subgroups, there is no hint of an added benefit of daratumumab versus watchful waiting; an added benefit is therefore not proven for patients with a low or intermediate risk according to the Mayo risk criteria with regard to this outcome.

Appetite loss

There is a statistically significant effect modification by the characteristic of age for the outcome of appetite loss. For patients aged < 65 years, there was a statistically significant difference in favour of daratumumab versus watchful waiting. For patients aged < 65 years, there is a hint of an added benefit of daratumumab versus watchful waiting. No statistically significant difference was shown between the study arms for patients ≥ 65 years, however. For this subgroup, there is no hint of an added benefit of daratumumab versus watchful

waiting; an added benefit is therefore not proven for patients aged ≥ 65 years with regard to this outcome.

Side effects

Severe AEs (CTCAE grade ≥ 3)

There is a statistically significant effect modification by the characteristic of sex for the outcome of severe AEs. A statistically significant difference to the disadvantage of daratumumab versus watchful waiting was shown for men. For men, there is a hint of greater harm of daratumumab in comparison with watchful waiting. For women, however, there was no statistically significant difference between the study arms. For this subgroup, there is no hint of greater or lesser harm of daratumumab in comparison with watchful waiting; greater or lesser harm for women is therefore not proven in this outcome.

Respiratory, thoracic and mediastinal disorders (AEs)

For the outcome of respiratory, thoracic and mediastinal disorders (AEs), there is a statistically significant effect modification by the characteristic of sex. A statistically significant difference to the disadvantage of daratumumab versus watchful waiting was shown for women. For women, there is a hint of greater harm of daratumumab in comparison with watchful waiting. For men, however, there was no statistically significant difference between the study arms. For this subgroup, there is no hint of greater or lesser harm of daratumumab in comparison with watchful waiting; greater or lesser harm for men is therefore not proven in this outcome.

I 5 Probability and extent of added benefit

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

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

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Chapter I 4 (see Table 17).

Determination of the outcome category for symptom outcomes

For the symptom outcomes below, it cannot be inferred from the dossier whether they are serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Symptoms

For the symptom outcomes (nausea and vomiting, and appetite loss, recorded using the EORTC QLQ-C30), insufficient severity data were available which would allow a classification as serious/severe. The symptom outcomes were therefore assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Table 17: Extent of added benefit at outcome level: daratumumab vs. watchful waiting (multipage table)

Outcome category Outcome Effect modifier Subgroup	daratumumab vs. no intervention Median time to event (months) Effect estimation [95% CI]; p-value Probability ^a	Derivation of extent ^b
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	No suitable data ^c	Lesser benefit not proven / added benefit not proven
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30 – time to first deterioration by ≥ 10 points)		
Fatigue	10.22 vs. 13.73 HR: 0.88 [0.69; 1.13]; p = 0.321	Lesser benefit not proven / added benefit not proven
Nausea and vomiting Risk according to Mayo criteria		
Low	NA vs. NA HR: 2.63 [0.97; 7.15] p = 0.058	Lesser benefit not proven / added benefit not proven
Intermediate	68.24 vs. 67.68 HR: 0.88 [0.51; 1.54] p = 0.666	Lesser benefit not proven / added benefit not proven
High	67.71 vs. 33.15 HR: 0.47 [0.28; 0.81] p = 0.007 Probability: hint	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ Added benefit, extent: minor
Pain	25.23 vs. 14.72 HR: 0.73 [0.57; 0.95] p = 0.020	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Lesser benefit not proven / added benefit not proven ^d
Dyspnoea	60.72 vs. 31.11 HR: 0.71 [0.53; 0.97] p = 0.031	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Lesser benefit not proven / added benefit not proven ^d
Insomnia	35.48 vs. 26.51 HR: 0.91 [0.69; 1.21]; p = 0.509	Lesser benefit not proven / added benefit not proven

Table 17: Extent of added benefit at outcome level: daratumumab vs. watchful waiting (multipage table)

Outcome category Outcome Effect modifier Subgroup	daratumumab vs. no intervention Median time to event (months) Effect estimation [95% CI]; p-value Probability ^a	Derivation of extent ^b
Appetite loss		
Age		
< 65 years	NA vs. 49.71 HR: 0.45 [0.27; 0.73] p = 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ Added benefit, extent: considerable
≥ 65 years	36.24 vs. 60.68 HR: 1.37 [0.88; 2.15] p = 0.164	Lesser benefit not proven / added benefit not proven
Constipation	63.77 vs. 49.51 HR: 0.85 [0.62; 1.16] p = 0.309	Lesser benefit not proven / added benefit not proven
Diarrhoea	NA vs. 50.63 HR: 0.94 [0.68; 1.31] p = 0.723	Lesser benefit not proven / added benefit not proven
Health status (time to first deterioration)		
EQ-5D VAS	60.85 vs. 55.20 HR: 0.83 [0.61; 1.14] p = 0.256	Lesser benefit not proven / added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 (time to first deterioration)		
Global health status	29.37 vs. 18.96 HR: 0.76 [0.58; 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
Physical functioning	41.76 vs. 30.69 0.83 [0.63; 1.10] p = 0.190	Lesser benefit not proven / added benefit not proven
Role functioning	19.25 vs. 20.47 HR: 0.89 [0.68; 1.15] p = 0.365	Lesser benefit not proven / added benefit not proven
Emotional functioning	53.95 vs. 29.77 HR: 0.69 [0.51; 0.92] p = 0.012 Probability: hint	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Added benefit, extent: minor

Table 17: Extent of added benefit at outcome level: daratumumab vs. watchful waiting (multipage table)

Outcome category Outcome Effect modifier Subgroup	daratumumab vs. no intervention Median time to event (months) Effect estimation [95% CI]; p-value Probability ^a	Derivation of extent ^b
Cognitive functioning	50.76 vs. 28.09 HR: 0.77 [0.57; 1.02] p = 0.070	Lesser benefit not proven / added benefit not proven
Social functioning	49.81 vs. 38.80 HR: 0.87 [0.65; 1.16]; p = 0.338	Lesser benefit not proven / added benefit not proven
Side effects		
SAEs	NA vs. NA 1.47 [0.97; 2.22] p = 0.071	Greater/lesser harm not proven
Severe AEs Sex Male	30.16 vs. NA HR: 1.93 [1.21; 3.08] HR: 0.52 [0.32; 0.83] ^e p = 0.006 Probability: hint	Outcome category: serious/severe side effects 0.75 ≤ CI _u < 0.90 or CI _u < 0.75, risk < 5% Greater harm, extent: considerable
Female	NA vs. NA HR: 0.87 [0.53; 1.44] p = 0.592	Greater/lesser harm not proven
Discontinuation due to AEs	No suitable data ^c	Greater/lesser harm not proven
General disorders and administration site conditions (AEs)	4.96 vs. NA HR: 3.40 [2.48; 4.67] HR: 0.29 [0.21; 0.40] ^e p < 0.001 Probability: hint	Outcome category: non-serious/non-severe side effects CI _u < 0.80 Greater harm, extent: considerable
Gastrointestinal disorders (AEs)	10.88 vs. NA HR: 3.10 [2.23; 4.29] HR: 0.32 [0.23; 0.45] ^e p < 0.001 Probability: hint	Outcome category: non-serious/non-severe side effects CI _u < 0.80 Greater harm, extent: considerable
Nervous system disorders (AEs)	32.89 vs. NA HR: 2.73 [1.90; 3.92] HR: 0.37 [0.26; 0.53] ^e p < 0.001 Probability: hint	Outcome category: non-serious/non-severe side effects CI _u < 0.80 Greater harm, extent: considerable

Table 17: Extent of added benefit at outcome level: daratumumab vs. watchful waiting (multipage table)

Outcome category Outcome Effect modifier Subgroup	daratumumab vs. no intervention Median time to event (months) Effect estimation [95% CI]; p-value Probability ^a	Derivation of extent ^b
Respiratory, thoracic and mediastinal disorders (AEs)		
Sex		
Male	NA vs. NA HR: 1.62 [0.96; 2.72] p = 0.069	Greater/lesser harm not proven
Female	23.06 vs. NA HR: 3.89 [2.23; 6.78] HR: 0.26 [0.15; 0.45] ^e p < 0.001 Probability: hint	Outcome category: non-serious/non-severe side effects CI _u < 0.80 Greater harm, extent: considerable
Skin and subcutaneous tissue disorders (AEs)	NA vs. NA HR: 4.48 [2.73; 7.33] HR: 0.22 [0.14; 0.37] ^e p < 0.001 Probability: hint	Outcome category: non-serious/non-severe side effects CI _u < 0.80 Greater harm, extent: considerable
Insomnia (AEs)	NA vs. NA HR: 9.48 [3.75; 23.97] HR: 0.11 [0.04; 0.27] ^e p < 0.001 Probability: hint	Outcome category: non-serious/non-severe side effects CI _u < 0.80 Greater harm, extent: considerable
Vascular disorders (AEs)	NA vs. NA HR: 2.35 [1.43; 3.85] HR: 0.43 [0.26; 0.70] ^e p < 0.001 Probability: hint	Outcome category: non-serious/non-severe side effects CI _u < 0.80 Greater harm, extent: considerable
Ear and labyrinth disorders (AE)	NA vs. NA HR: 3.61 [1.46; 8.95] HR: 0.28 [0.11; 0.68] ^e p = 0.006 Probability: hint	Outcome category: non-serious/non-severe side effects CI _u < 0.80 Greater harm, extent: considerable
Infections and infestations (severe AEs)	NA vs. NA HR: 3.71 [1.74; 7.93] HR: 0.27 [0.13; 0.57] ^e p < 0.001 Probability: hint	Outcome category: serious/severe side effects CI _u < 0.75, risk ≥ 5% Greater harm, extent: major

Table 17: Extent of added benefit at outcome level: daratumumab vs. watchful waiting (multipage table)

Outcome category Outcome Effect modifier Subgroup	daratumumab vs. no intervention Median time to event (months) Effect estimation [95% CI]; p-value Probability ^a	Derivation of extent ^b
a. Probability provided if there is a statistically significant and relevant effect. b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u). c. See Section I 4.1. d. The extent of the effect in this non-serious/non-severe outcome was no more than marginal. e. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit. AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; NA: not achieved; QLQ-C30: Quality of Life Questionnaire-Core 30; SAE: serious adverse event; VAS: visual analogue scale		

I 5.2 Overall conclusion on added benefit

Table 18 summarizes the results taken into account for the overall conclusion on the extent of the added benefit.

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

Positive effects	Negative effects
Outcomes with observation over the entire study duration	
–	–
Outcomes with shortened observation period	
Non-serious/non-severe symptoms/late complications ▪ Nausea and vomiting: ▫ Risk according to the Mayo criteria (high) - hint of an added benefit – extent: minor ▪ Appetite loss: ▫ Age (< 65 years) - hint of an added benefit – extent: considerable	–
Health-related quality of life ▪ Global health status: hint of an added benefit – extent: minor ▪ Emotional functioning: hint of an added benefit – extent: minor	–
–	Serious/severe side effects ▪ Severe AEs ▫ Sex (male): hint of greater harm – extent: considerable ▪ Infections and infestations (severe AEs): hint of greater harm – extent: major
–	Non-serious/non-severe side effects ▪ Hint of greater harm – extent: considerable ▫ General disorders and administration site conditions (AEs) ▫ Gastrointestinal disorders (AEs) ▫ Nervous system disorders (AEs) ▫ Respiratory, thoracic and mediastinal disorders (AEs) - Sex (female) ▫ Skin and subcutaneous tissue disorders (AEs) ▫ Insomnia (AE) ▫ Vascular disorders (AEs) ▫ Ear and labyrinth disorders (AE)
AE: adverse event	

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

In terms of positive effects, there is an added benefit of minor extent in the category of health-related quality of life, in the outcomes of global health status and emotional functioning. In addition, there is a minor added benefit for the outcome of nausea and vomiting in patients with a high risk of disease progression according to the Mayo risk criteria, and a considerable added benefit for the outcome of appetite loss in patients aged < 65 years.

On the other hand, there are a multitude of negative effects in the side effects category, which have major and considerable extent. There is greater harm of major extent for the outcome of infections and infestations (severe AEs), and, for men, considerable harm in terms of the overall rate of severe AEs. Furthermore, there are disadvantages of considerable extent of daratumumab in 8 non-serious/non-severe specific AEs. Overall, many patients in the intervention arm were affected by these AEs. For example, more than twice as many patients in the intervention arm (approx. 60% versus < 30%) had general disorders and administration site conditions and gastrointestinal disorders. Approximately half of the patients in the intervention arm had nervous system disorders (approx. 49% versus 22%).

In summary, there is no hint of an added benefit of daratumumab versus the ACT for adult patients with smouldering multiple myeloma who are at high risk of developing multiple myeloma.

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

Table 19: Daratumumab – probability and extent of added benefit

Therapeutic indication	ACT ^a	Probability and extent of added benefit
Adult patients with smouldering multiple myeloma who are at high risk of developing multiple myeloma	Watchful waiting	Added benefit not proven
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

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

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

I 6 References for English extract

Please see full dossier assessment for full reference list.

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

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