# Evidence report

# Smouldering multiple myeloma (high-risk)

## Daratumumab or active monitoring?

Version 1

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## LIST OF ABBREVIATIONS

AE: Adverse events
AMNOG: Pharmaceuticals Market Reorganisation Act
ASCT: Autologous stem cell transplantation
BMPC: Bone marrow plasma cells
CI: Confidence interval
CT: Computer tomography
DA: Decision aid
EORTC QLQ: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D: EuroQol Five Dimension Five Level Questionnaire
FAQ: Frequently asked question
FDA: Food and Drug Administration
HR: Hazard ratio
HrQoL: Health-related quality of life
HTA: Health technology assessment
Ig: Immunoglobulin
IMWG: International Myeloma Working Group
IQWiG: Institute for Quality and Efficiency in Health Care
MGUS: Monoclonal gammopathy of undetermined significance
MM: Multiple myeloma
MRI: Magnetic Resonance Imaging
OIS: Optimal information size
PET-CT: Positron Emission Tomography/Computed Tomography
PICOS: Participants, intervention, comparators, outcomes, and study design
RCT: Randomised controlled trial
RD: Risk difference
RoB: Risk of bias
SDM: Shared decision making
sFLC: Serum free light chain
SMM: Smouldering multiple myeloma
VAS: Visual Analogue Scale

## PROJECT OBJECTIVES

A key aim of the project is to inform patients on different therapy options as part of shared decision making (SDM). This evidence report is prepared to inform an evidence-based online decision aid (DA) which addresses patients with high-risk smouldering multiple myeloma (SMM). The report relies on teamwork with clinical experts from two German university medical centres and patients from patient organizations.

## INTRODUCTION TO THE CONDITION

SMM is considered to be a transitional stage between monoclonal gammopathy of undetermined significance (MGUS) and active multiple myeloma (MM). In patients with SMM, myeloma cells can be detected in the bone marrow and paraproteins are found in blood and/or urine (Table 1). However, patients are asymptomatic and the diagnostic criteria for myeloma are not met [1].

Table 1: Diagnostic criteria for SMM [2]

| **Criteria** | **SMM** |
|---|---|
| Monoclonal protein | Serum monoclonal protein (IgG or IgA) ≥ 30g/L or urinary monoclonal protein ≥ 500mg per 24h **and/or** |
| Clonal bone marrow plasma cells | 10-60% **and** |
| Myeloma defining events | Absence of myeloma-defining events [a] or amyloidosis |
| [a] according to SLiM/CRAB criteria, see Table 7 | |

SMM is a heterogenous condition with varying transition rates to active myeloma. The International Myeloma Working Group (IMWG) has developed revised criteria for risk stratification based on three independent factors: serum M-protein >2 g/dL, involved to uninvolved free light-chain ratio >20, and marrow plasma cell infiltration >20%. Cytogenetic abnormalities can be included for further stratification. Depending on the number of risk factors, patients are categorized into low, intermediate, and high-risk groups [3]. There are, however, also other risk classification systems which might lead to discordant assessments whether patients have high-risk SMM [4].

Patients with high-risk SMM have a higher risk of progression than patients with low- or intermediate-risk SMM. However, the progression rates depend on the follow-up time and may vary individually. Even patients with high-risk SMM may not experience progression within their lifetime.

Until recently, patients with SMM were usually only offered active monitoring to detect transition to active MM. Especially for high-risk patients, however, there were some indications that treatment might delay transition to active myeloma [5]. Daratumumab is so far the only medicine authorised for the treatment of SMM.

## METHODS

Before preparing the evidence report, we conducted a scoping process with the clinical experts. Together we defined the characteristics of participants, intervention, comparators, outcomes, and study design (PICOS), used as inclusion criteria for the evidence report, as well as the frequently asked questions (FAQs) which the DA should answer. The FAQs were checked against the needs assessment conducted with patients and adapted where necessary.

### INCLUSION CRITERIA

This decision aid only applies to patients with SMM. For patients with active MM, there are separate DAs. The inclusion and exclusion criteria, according to PICOS, are described in Table 2

Table 2: Inclusion and exclusion criteria

| | **Included** | **Excluded** |
|---|---|---|
| Population | Patients with high-risk smouldering myeloma (SMM), any definition of high-risk | low-risk or intermediate-risk SMM, active multiple myeloma according to IMWG criteria, MGUS, diseases with monoclonal immunoglobulin disposition, solitary plasmacytoma |
| Intervention | Daratumumab monotherapy | Interventions without marketing authorization |
| Comparator | Active monitoring | n.a. |
| Outcomes | progression to active multiple myeloma (according to IMWG criteria); time to progression; need for subsequent myeloma therapy; time to subsequent myeloma therapy; quality of life, overall survival; adverse events (AE): serious and severe AE, discontinuation due to AE | n.a. |
| Study design | Stepwise approach: Guidelines, systematic reviews, randomised controlled trials (confirmatory trials) | n.a. |

n.a.= not applicable; SMM: smouldering myeloma; IMWG: International Myeloma Working Group; MGUS: monoclonal gammopathy of undetermined significance; AE: adverse events

### FREQUENTLY ASKED QUESTIONS

The frequently asked questions (FAQs) underpinning the literature searches were developed in collaboration with clinical experts during the scoping-process and aligned with patients'

information needs as reported in the needs' assessment. The following FAQs were identified:

- FAQ 1: What does the treatment involve?
- FAQ 2: Will I live longer?
- FAQ 3: Does the treatment prevent progression to active myeloma?
- FAQ 4: How will the treatment impact my quality of life?
- FAQ 5: What are the short- or long-term risks or side effects?
- FAQ 6: How do I know that the treatment works?
- FAQ 7: How does the treatment impact my daily life?

#### LITERATURE SEARCHES

Our literature search followed a pragmatic stepwise approach. As the treatment of multiple myeloma is a rapidly evolving field, we restricted the search for evidence syntheses to years 2021 to 2025.

- First, we searched for evidence-based guidelines which are suitable for data extraction.
- If we did not find any suitable references, we proceeded to health technology assessment (HTA) reports, including dossiers according to the Pharmaceuticals Market Reorganisation Act (AMNOG) when these provided more detailed analyses.
- If these searches were futile or the retrieval insufficient to answer the FAQs, we proceeded to systematic reviews.
- To cover the latest evidence, we additionally searched for recent publications of randomised controlled trials and results in study registries.
- We supplemented the systematic searches by handsearching where necessary.

The search strategies are described in detail in Appendix 1.

For the description of the condition and the treatment options, we hand searched the websites of relevant and reliable medical professional and patient organisations in Germany and selected other countries.

#### *Handling of citations*

Identified references from the bibliographic database searches were downloaded as RIS files and transferred into Rayyan App for abstract screening. Excluded references were tagged with the reasons for exclusion. Results of the abstract screening were exported as RIS file. Results of the full text screening were documented in Appendix 1.

#### *Quality assurance within the search process*

One reviewer (IH) developed the search strategy, a second reviewer (JP) checked the strategy according to the PRESS Peer Review of Electronic Search Strategies Checklist [5].

### Methods of study selection

One reviewer (IH) inspected the title and abstract of each reference identified by the search and documented reasons for exclusion. For potentially relevant articles, the full article was obtained, inspected, and inclusion criteria applied. Reasons for exclusion were documented. All decisions were checked by a second reviewer (JP). Any disagreements were resolved through discussion.

### Methods of data extraction

For the data extraction, we preferred evidence syntheses, followed by the source with the most recent data cut-off and/or most detailed and/or relevant data to answer the FAQ. For each study, data were extracted by one reviewer (IH) and checked by another (JP). Any disagreements were resolved through discussion.

### Methods for appraising risk of bias and certainty of the evidence

For the risk of bias (RoB) assessment, we used Risk Of Bias instrument for Use in SysTematic reviews-for Randomised Controlled Trials (ROBUST-RCT) for randomised controlled trials (RCT) [6]. Due to the high-quality methods and quality assurance procedures, risk of bias was not formally assessed for reports prepared by the Institute for Quality and Efficiency in Health Care (IQWiG). We adopted the available risk of bias assessment of these reports for the included trials.

Certainty of the identified evidence is presented using the GRADE approach which assesses risk of bias, publication bias, imprecision, inconsistency, and indirectness according to the assessment criteria published by the GRADE working group [7].

The certainty of the evidence is rated as follows:

- High certainty: Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate certainty: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low certainty: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low certainty: We are very uncertain about the estimate.

Where systematic reviews or other evidence syntheses presented risk of bias and/or GRADE assessments, we adopted the ratings for the evidence report.

One reviewer (IH) checked the risk of bias and rated the certainty of the evidence. The results were checked by a second reviewer (JP). Any disagreements were resolved through discussion.

# RESULTS

## LITERATURE SEARCHES AND INCLUSION ASSESSMENT

Our database searches for guidelines and HTA reports did not retrieve suitable references. By hand searching, we identified a HTA report (IQWiG report) [6] and the corresponding AMNOG dossier [7] which contain data from the AQUILA trial. Therefore, we did not further search for systematic reviews. However, we searched for newer RCTs. We did not find additional trials, but included the journal publication of the AQUILA for the study protocol and possibly further results beyond the IQWiG report [8]. We also included a FDA briefing document for supplemental analyses of the AQUILA trial [9].

For the description of the treatment, we included material from Myeloma UK [10].

## RISK OF BIAS ASSESSMENT

We adopted the risk of bias assessments from the IQWiG report. Risk of bias was rated as high for all outcomes. However, for overall survival, the IQWiG did not assess risk of bias due to inadequate data. Based on the information in the IQWiG report, we added own risk of bias assessments for overall survival as well as progression (not rated in the IQWiG report). For overall survival and progress, risk of bias was rated as high and low, respectively (see Appendix 2).

## OVERVIEW OF THE EVIDENCE

### *Description of the trial*

The ongoing AQUILA trial (NCT03301220) recruited patients in 2017 to 2019 and included 390 patients between 31 and 86 years (median age 64 years) which were randomised to treatment (daratumumab monotherapy until progression or up to 36 months, whichever occurred first) or to active monitoring. The trial is expected to be completed in June 2026.

The main inclusion criterion was smouldering multiple myeloma classified as high risk. However, the inclusion criteria were broader than the risk stratification criteria which are used most commonly nowadays (Mayo 2018 or IMWG 2020, see Table 3). Only 41 % of the study population in AQUILA would be classified as high-risk according to Mayo 2018 criteria. The proportion according to IMWG 2020 criteria is not known.

Comprehensive data is available for the subgroup which corresponds to high-risk SMM according to Mayo 2018 criteria (post-hoc subgroup analysis). As this subgroup is similar to patients for whom the DA might be used, we report data not only for the full study population, but also from the subgroup analysis throughout this evidence report. It should be noted, however, that there was no indication of an effect modification (statistical interaction) for the subgroup for any outcome. Therefore, if there is a statistically significant difference between the groups for the full study population, but not for the subgroup, results should be interpreted in the light of the fewer events in the subgroup and the lack of interaction, i.e. they might be attributed to a lack of power.

Table 3: Comparison of risk stratification criteria

| Aspect | **AQUILA** [8] | **Mayo 2018** [4] | **IMWG 2020** [4] |
|---|---|---|---|
| Minimum criteria for high risk SMM | Clonal BMPC ≥ 10% **and** at least 1 of the following risk factors: | At least 2 of the following risk factors: | At least 3 of the following risk factors: |
| BMPC (%) | >50% to <60% with measurable disease | > 20 | > 20 |
| sFLC ratio | ≥8 and <100 | <0.05 or >20 | >20 |
| M-protein (g/dL) | ≥ 3 | >2 | >2 |
| Cytogenetics | n.a. | n.a. | High-risk abnormalities present |
| IgA SMM | present | n.a. | n.a. |
| Immunoparesis | reduction of 2 uninvolved immunoglobulin isotypes | n.a. | n.a. |
| IMWG: International Myeloma Working Group; SMM: smouldering myeloma; BMPC: bone marrow plasma cells; sFLC: serum free light chain; Ig: immunoglobulin; n.a.: not applicable | | | |

*Description of the evidence sources*

All evidence sources report data for the clinical cut-off date 01.05.2024. Median time on treatment was 35 months with daratumumab and 25.9 months in the active monitoring group. The IQWiG report [6] does not contain data on the outcomes overall survival, EORTC QLQ-MY20, discontinuation due to adverse events and (time to) progression. These data are, however, available in the AMNOG dossier [7] and the journal publication [8]. The journal publication also provides the study protocol in the online supplement.

Table 4 summarises the sources of evidence used to answer the FAQs. FAQs 6 and 7 have not been included in the table as the answers will be derived from data progression including development of symptoms (FAQ 3) and description of the treatments (FAQ 1). For the description of the treatments, we used information from Myeloma UK [10] and the journal publication of the AQUILA trial.

Table 4: Overview of the evidence sources

| **Trial [Reference]** | **FAQ1: Treatment modalities** | **FAQ2: Survival** | **FAQ3: Progression** | **FAQ4: Quality of life** | **FAQ5: Side effects** |
|---|---|---|---|---|---|
| IQWiG report AQUILA [6] | | | | ✓ | ✓ |
| AMNOG dossier AQUILA [7] | | ✓ | ✓ | ✓ | ✓ |

| | | | | | |
|---|---|---|---|---|---|
| Dimopoulos 2025 [8] | ✓ | ✓ | ✓ | ✓ | ✓ |
| Myeloma UK Treatment Guide [10] | ✓ | | | | ✓ |

## FAQ 1: What does the treatment involve?

### *Daratumumab*

The aim of the treatment with daratumumab is to delay progression to active myeloma [8].

Daratumumab is a CD38 antibody. The drug binds to specific proteins on the surface of the myeloma cells which leads to the death of myeloma cells. It is given by slow injection over several minutes at the doctor's office [10].

The drug is given in cycles of 4 weeks each. Injections are weekly in cycles 1 and 2, every other week in cycles 3 to 6 and every 4 weeks thereafter for a maximum of 3 years or until progression to active multiple myeloma. To avoid injection reactions, pre-dose and post-dose medication is required, usually involving an antipyretic, an antihistamine and a corticosteroid. Also preventive medicine for herpes zoster reactivation is recommended [8].

### *Active monitoring*

The aim of active monitoring is to detect progression to active myeloma as early as possible [1].

In the AQUILA trial, patients in the comparison group were monitored for progression every 3 months [8]. Current guidelines, however, give no detailed guidance for the monitoring intervals in patients with high-risk smouldering myeloma. The EHA/EMN guideline recommends every 6 months for patients with low-risk SMM and every 3–6 months for patients with intermediate-risk SMM but does not mention high-risk SMM [11]. A Good Practice Paper by the British Society for Haematology recommends clinical trial entry for high-risk patients or otherwise 3-monthly monitoring for 5 years [4].

At the check-ups, patients are asked about any disease symptoms, e.g. (bone) pain, fatigue, unexpected weight loss, frequent infections. Additionally, there will be checks of urine and blood to check renal function and blood parameters. When symptoms occur between regular check-ups, patients should consult their doctor without delay. In larger intervals or when there are signs of progression, additional imaging might be included in the check-ups. Bone marrow biopsies might be performed on a case-by-case basis [1].

### *Supportive care*

Besides psychological support, patients should receive advice about infection risk and be advised about vaccinations. Other prophylactic medicines, however, are only recommended in special situations. Bisphosphonates and thrombosis prophylaxis are not routinely recommended in patients with SMM [4].

*Subsequent therapy after progression*

For the time being, there are no guideline recommendations about subsequent therapy after progression when SMM has been treated with daratumumab.

If there is no progression during treatment, but only after a longer period after the end of the treatment, daratumumab can be part of first-line therapy once active myeloma is diagnosed (e.g. as part of a quadruplet) [8].

When SMM progresses to active myeloma during treatment with daratumumab or within 60 days after the end of the treatment, however, the disease might be considered CD38 refractory [12,13]. In this case, CD38 antibodies might not be used as part of first-line therapy. It should be noted that a quadruplet including a CD38 antibody is recommended as the most effective first-line therapy (if suitable, as induction therapy before autologous stem cell transplantation) by the EHA-EMN guidelines [11].

*Conclusion for the decision aid*

- The DA should describe the treatment and active monitoring as explained above.
- There might be some variance in clinical practice for active monitoring. Therefore, the DA should point out that patients should discuss all details with their doctor.
- The DA should also explain consequences for subsequent therapy.

### FAQ 2: Will I live longer?

Information on overall survival in the AQUILA trial is available for the full study population as well as the subgroup high-risk according to Mayo 2018 criteria (
Table 5).

Table 5: Overall mortality

| Population | Daratumumab<br>Proportion<br>Median time to event | Active monitoring<br>Proportion<br>Median time to event | Effect |
|---|---|---|---|
| Full study population [7][a]<br>n = 390 | 8 per 100<br>n.r. | 13 per 100<br>n.r. | HR 0.52<br>(0.27;0.98)<br>RD 5 per 100 |
| Subgroup high risk Mayo 2018 [7][b]<br>n = 158 | 14 per 100<br>n.r. | 16 per 100<br>n.r. | HR 0.78 (0.34; 1.75)<br>RD 2 per 100 |

Median follow-up: 66 months with daratumumab, 65 months with active monitoring. Effect sizes are reported as point estimate and 95% confidence interval.
[a] Table 4-20. 15 events with daratumumab, 26 events with active monitoring
[b] Appendix 4-H, Table 4-1. 10 events with daratumumab, 14 events with active monitoring
n.r. not reached; HR: hazard ratio, RD: risk difference.

Proportions for overall mortality are higher in the subgroup than in the full study population which is biologically plausible. However, the point estimates indicate a higher risk reduction for the full population (HR 0.52, 5 per 100) than with the subgroup (HR 0.78, 2 per 100). Whereas the difference is statistically significant for the full population (however, with an upper limit of the confidence interval near the null effect), it is not for the subgroup.

This might be a result of the small number of events, especially for the subgroup. For the final data cut-off of the AQUILA trial, 107 events for the outcome overall survival in the full study population are estimated [7]. For the current data cut-off, only 41 events have occurred for the full study population and 24 for the subgroup. It should be noted that the results so far also do not preclude the possibility that certain patients in the high-risk group do not benefit from daratumumab monotherapy due to the aggressive nature of their condition. However, it is difficult to draw final conclusions on overall survival for the time being.

Additionally, the certainty of the evidence is hampered by the fact that subsequent therapy was insufficient in the active monitoring arm: Only a third of the patients with subsequent therapy received a CD38 antibody which would have been standard of care as part of a quadruplet. The IQWiG report therefore considers the results for overall survival as not interpretable and does not acknowledge an added benefit of daratumumab.

Table 6: GRADE assessment: overall mortality

| Aspect | Downgrading | Certainty | Notes |
|---|---|---|---|
| Study type | | High | RCT |
| ROB | ↓ | | See Appendix 2 (due to insufficient subsequent therapy) |
| Imprecision | ↓↓ | | For subgroup: Difference is not statistically significant for subgroup; CI includes important benefit/harm (about 70% risk reduction or increased risk) = downgrading twice<br>For full study population: Difference is statistically significant; effect size is large (HR 0.52), but ratio of upper and lower limit CI > 3 = downgrading twice |
| Indirectness | n.a. | | No concern for subgroup |
| Inconsistency | n.a. | | Single trial only |
| Publication bias | n.a. | | No concern according to IQWiG report |
| **Overall** | ↓↓↓ | **Very low** | |

RCT: randomised controlled trial; CI: confidence interval

*Conclusion for the decision aid*

- There is considerable uncertainty whether treatment with daratumumab lowers overall mortality compared to active monitoring.
- For the full study population, there might be better overall survival with daratumumab. However, there is uncertainty about the applicability of the results to patients with high-risk SMM according to recent definitions: For the subgroup high-risk according to Mayo 2018 (corresponding to the target group of the DA), there is no statistically significant difference between the groups. However, it should be noted, that the data for overall mortality in the subgroup relies on very few events and the confidence interval includes both important benefit and important harm.
- Additionally, the data for overall survival is not easy to interpret due to insufficient subsequent therapy in the active monitoring group.
- The certainty of the evidence is very low.
- In the face of the uncertainty, the DA should not communicate effect sizes.

### FAQ 3: Does the treatment prevent progression to active myeloma?

Diagnosis of active multiple myeloma has been defined in the AQUILA trial according to IMWG criteria for the diagnosis for multiple myeloma (SLiM/CRAB criteria, Table 7). We report the results for the operationalisation "time to diagnosis of myeloma" as analysed in the AMNOG dossiers, as this operationalisation is easier to interpret than the primary endpoint progression free survival.

Table 7: SLiM/CRAB criteria for the diagnosis of multiple myeloma (IMWG) [8]

| | |
|---|---|
| Clonal BMPCs ≥10% or biopsy-proven bony or extramedullary plasmacytoma AND<br>≥1 of the below multiple myeloma–defining events | |
| CRAB criteria (evidence of end organ damage) | **C**alcium elevation: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal of >2.75 mmol/L (>11 mg/dL) |
| | **R**enal insufficiency: creatinine clearance 177 µmol/L (>2 mg/dL) |
| | **A**naemia: haemoglobin value >20 g/L below the limit of normal or a haemoglobin value |
| | **B**one disease: ≥1 osteolytic lesions on skeletal radiography, CT, or PET-CT |
| SLiM criteria (biomarkers) | Clonal BMPCs: ≥60% (**s**ixty) |
| | Serum free **li**ght chains: ratio of involved and uninvolved serum free light chains (sFLC) ≥100 |
| | >1 focal lesions on **M**RI studies |
| IMWG: International Myeloma Working Group; BMPC: bone marrow plasma cells; CT: computer tomography; PET-CT: Positron Emission Tomography/Computed Tomography; MRI: Magnetic Resonance Imaging | |

The IQWiG report does not acknowledge progression as a patient-relevant outcome and analyses increasing symptoms of the disease and worsening health status instead [6].

#### *Diagnosis of myeloma*

For both the full study population and the subgroup with high-risk according to the Mayo 2018 criteria, the time to progression is statistically significantly lower with daratumumab than with active monitoring as indicated by the hazard ratios (Table 8). With similar follow-up in both trial arms, the proportion of patients with progression is lower with daratumumab than with active monitoring (statistical significance for the difference of proportions not reported). The treatment effect (both in absolute and relative terms) is higher for the subgroup than the full study population which is biologically plausible. After about five years, approximately one third of the patients in the subgroup had progression despite treatment with daratumumab, while one third of the patients with active monitoring remained free of progression to myeloma.

Median time to progression, however, has not been reached for the daratumumab arms in the full study population and the in the subgroup. In the active monitoring arm, the median time to progression is 39 months for the full study population and 22 months for the subgroup. The faster progression in the subgroup is biologically plausible.

Table 8: Diagnosis of myeloma

| Population | Daratumumab<br>Proportion<br>Median time to event | Active monitoring<br>Proportion<br>Median time to event | Effect |
|---|---|---|---|
| Full study population [7][a]<br>n = 390 | 32 per 100<br>n.r. | 51 per 100<br>39 months | HR 0.45 (0.33; 0.62)<br>RD 19 per 100 |
| Subgroup high risk Mayo 2018 [7][b]<br>n = 158 | 33 per 100<br>n.r. | 65 per 100<br>22 months | HR 0.31 (0.19; 0.51)<br>RD 32 per 100 |
| Median follow-up: 66 months with daratumumab, 65 months with active monitoring. Effect sizes are reported as point estimate and 95% confidence interval.<br>[a] Table 4-23<br>[b] Appendix 4-H, Table 4-2<br>n.r. not reached; HR: hazard ratio; RD: risk difference. | | | |

The journal publication ([8], Table 2) indicates, however, that most progression events were biochemical rather than clinical. There were no cases of renal insufficiency and only few events of anaemia and bone disease. As a report of the U.S. Food and Drug Administration (FDA) points out, about 30 % of patients progressed based on SLiM criteria alone, whereas clinical myeloma-defining events (CRAB) were only found in 12 % of the patients. In an analysis of the clinical events, anaemia events were minor as no patient needed a blood transfusion and bone events were mainly asymptomatic and primarily identified by imaging. This means that it is unclear whether the delay in progression is clinically meaningful [9].

The FDA report also points out that there was no benefit in the daratumumab arm for progression on next line of therapy. Although data are not mature, the FDA report concludes that the value of treatment prior to development of disease is questionable [9].

The FDA analysis relies on the full study population. It might be possible that the proportion of patients with symptomatic disease in the high-risk subgroup might be higher than in the full study population. The respective analyses for the subgroup high-risk according to Mayo 2018 criteria, however, are not available.

### *Symptoms and health status*

Smouldering myeloma is by definition an asymptomatic condition although unspecific symptoms as fatigue might occur. When the disease progresses to full myeloma, symptoms may develop. This might also impact the health-related quality of life (HrQoL). The

treatment of SMM therefore aims to delay the development of symptoms and delay the worsening of HrQoL (see FAQ 4).

The AQUILA trial used the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) symptom scales for the assessment of symptoms and the EuroQol Five Dimension Five Level Questionnaire (EQ-5D) Visual Analogue Scale (VAS) for the assessment of health status. The investigators also included the domain disease symptoms of the myeloma-specific questionnaire EORTC QLQ-MY20. In the IQWiG report, results from EORTC QLQ-MY20 were not considered as not all domains were used in the trials.

It should be noted that the follow-up for patient-reported efficacy outcomes was originally 18 months after progression and has been shortened in a later amendment to the study protocol to 6 months after progression. As there were more cases of progression in the active monitoring group, median follow-up was shorter than in the daratumumab group: about 51 months with daratumumab and about 38 months in the active monitoring group. Also, there were differences in the frequency of assessments according to progression status: Besides at the time of screening as well as end of study, patients answered the questionnaires in week 12, week 24, week 60 and once per year thereafter. In case of progression, there were additional questionnaires after progression. This might lead to detection bias with changes noted earlier in the treatment arm with more progression [6].

In the AMNOG process, the minimal important ("relevant") difference has been defined as 10 points (10 %) for the respective items of EORTC QLQ-C30 and EORTC QLQ-MY20 and 15 points (15 %) for EQ-5D VAS. This definition is adopted for this evidence report. As the symptoms are non-specific and may also occur in the general population, both the IQWiG report and the AMNOG dossier describe this process as "worsening of symptoms". The AMNOG dossier also contains an operationalisation of "first relevant improvement". However, as SMM is by definition asymptomatic and the symptoms of myeloma are non-specific, we do not report this operationalisation.

The responder analyses for first relevant worsening can be found below (Table 9).

Table 9: First relevant worsening of symptoms

| Domain | Population | Daratumumab<br><br>Proportion<br>Median time to event | Active monitoring<br>Proportion<br>Median time to event | Effect |
|---|---|---|---|---|
| Fatigue | Full study population [6][a]<br>n = 390 | 66 per 100<br>10 months | 64 per 100<br>14 months | HR 0.88 (0.69; 1.13) |
| | Subgroup high risk Mayo 2018 [7][b]<br>n = 158 | 64 per 100<br>8 months | 61 per 100<br>14 months | HR 0.86 (0.57; 1.28) |
| Nausea/ vomiting | Full study population [6][a]<br>n = 390 | 34 per 100<br>68 months | 33 per 100<br>68 months | HR 0.78 (0.55; 1.11) |
| | Subgroup high risk Mayo 2018 [7][b]<br>n = 158 | 32 per 100<br>68 months | 41 per 100<br>33 months | HR 0.47 (0.28; 0.81) |
| Pain | Full study population [6][a]<br>n = 390 | 60 per 100<br>25 months | 60 per 100<br>15 months | HR 0.73 (0.57; 0.95) |
| | Subgroup high risk Mayo 2018 [7][b]<br>n = 158 | 63 per 100<br>17 months | 61 per 100<br>14 months | HR 0.69 (0.46; 1.04) |
| Dyspnoea | Full study population [6][a]<br>n = 390 | 43 per 100<br>61 months | 45 per 100<br>31 months | HR 0.71 (0.53; 0.97) |
| | Subgroup high risk Mayo 2018 [7][b]<br>n = 158 | 44 per 100<br>50 months | 44 per 100<br>25 months | HR 0.68 (0.42; 1.09) |
| Insomnia | Full study population [6][a]<br>n = 390 | 54 per 100<br>35 months | 47 per 100<br>27 months | HR 0.91 (0.69; 1.21) |
| | Subgroup high risk Mayo 2018 [7][b]<br>n = 158 | 50 per 100<br>36 months | 43 per 100<br>25 months | HR 0.87 (0.55; 1.38) |

| | | | | |
|---|---|---|---|---|
| Loss of appetite | Full study population [6][a]<br>n = 390 | 37 per 100<br>68 months | 38 per 100<br>58 months | HR 0.78<br>(0.56; 1.08) |
| | Subgroup high risk Mayo 2018 [7][b]<br>n = 158 | 40 per 100<br>61 months | 37 per 100<br>31 months | HR 0.79<br>(0.47; 1.32) |
| Obstipation | Full study population [6][a]<br>n = 390 | 42 per 100<br>64 months | 39 per 100<br>50 months | HR 0.85<br>(0.62; 1.16) |
| | Subgroup high risk Mayo 2018 [7][b]<br>n = 158 | 46 per 100<br>53 months | 36 per 100<br>50 months | HR 0.99<br>(0.60; 1.63) |
| Diarrhoea | Full study population [6][a]<br>n = 390 | 39 per 100<br>n.r. | 36 per 100<br>51 months | HR 0.94<br>(0.68; 1.31) |
| | Subgroup high risk Mayo 2018 [7][b]<br>n = 158 | 36 per 100<br>n.r. | 34 per 100<br>39 months | HR 0.93<br>(0.55; 1.58) |
| Health status [d] | Full study population [6][a]<br>n = 390 | 41 per 100<br>61 months | 40 per 100<br>55 months | HR 0.83<br>(0.61; 1.14) |
| | Subgroup high risk Mayo 2018 [7][c]<br>n = 158 | 42 per 100<br>n.r. | 38 per 100<br>63 months | HR 0.79<br>(0.48; 1.31) |
| Disease symptoms [e] | Full study population [7][f]<br>n = 390 | 52 per 100<br>36 months | 54 per 100<br>18 months | HR 0.72<br>(0.54; 0.94) |
| | Subgroup high risk Mayo 2018 [7][f]<br>n = 158 | 49 per 100<br>36 months | 50 per 100<br>18 months | HR 0.72<br>(0.46; 1.13) |

Median follow-up: approximately 51 months with daratumumab, 38 months with active monitoring. For the assessment, the EORTC QLQ-C30 was used if not otherwise noted. Effect sizes are reported as point estimate and 95% confidence interval.
n.r. not reached; HR: hazard ratio; RD: risk difference.
[a] Table 15
[b] Appendix 4-H, Table 4-8, first relevant worsening
[c] Appendix 4-H, Table 4-6, first relevant worsening
[d] EQ-5D VAS
[e] EORTC QLQ-MY20
[f] Appendix 4-H, Table 4-10

In the full study population, daratumumab delays worsening of symptoms better than active monitoring only for few symptoms in a statistically significant way: Pain (25 vs. 15 months), dyspnoea (61 vs. 31 months), and disease symptoms (36 vs. 18 months). For the subgroup high-risk according to Mayo 2018 criteria, statistically significant differences are noted for nausea/vomiting (68 vs. 33 months) only. However, for pain, dyspnoea and disease symptoms, effect estimates are very similar for the full study population and the subgroup. Therefore, it seems probable that the delay in worsening for some symptoms might also apply to the subgroup. The proportions cannot easily be compared due to differences in follow-up.

The IQWiG report [6] considers the benefit for pain and dyspnoea as too small in comparison to their clinical significance so that the added benefit is not even rated as minor. For nausea/vomiting, the IQWiG report acknowledges a minor added benefit for the subgroup high-risk according to Mayo 2018. Also acknowledged is a considerable added benefit in the domain loss of appetite for the subgroup of patients younger than 65 years (not discussed in this evidence report). The FDA report does not consider the patient-reported outcomes to be informative due to the sparse assessment and the questionable applicability of symptom scales to patients with an asymptomatic condition [9].

### *Time to first-line myeloma therapy*

Another measure of progression which is probably relevant for patients is the time until first-line myeloma therapy is initiated. This therapy usually involves a quadruplet with a CD38 antibody or autologous stem cell transplantation (ASCT) if this is suitable. The results for this outcome are reported in Table 10.

Table 10: Time to first-line myeloma therapy

| **Population** | **Daratumumab**<br>**Proportion**<br>**Median time to event** | **Active monitoring**<br>**Proportion**<br>**Median time to event** | **Effect** |
|---|---|---|---|
| Full study population [7][a]<br>n = 390 | 33 per 100<br>n.r. | 52 per 100<br>50 months | HR 0.46<br>(0.33; 0.62) |
| Subgroup high risk Mayo 2018 [7][a]<br>n = 158 | 39 per 100<br>n.r. | 64 per 100<br>28 months | HR 0.39<br>(0.25; 0.62) |
| Median follow-up: 66 months with daratumumab, 65 months with active monitoring. Effect sizes are reported as point estimate and 95% confidence interval.<br>[a] Appendix 4-H, Table 4-5<br>n.r. not reached; HR: hazard ratio; RD: risk difference. | | | |

In both the full study population as well as the subgroup, time to first-line myeloma therapy is longer for the daratumumab group as shown by the hazard ratios. However, median time has only been reached in the active monitoring group. It should be noted that the time to first-line myeloma therapy is considerably shorter in the subgroup (28 months) than in the full study population (50 months). However, this outcome is not easy to interpret as the choice of when and how to treat was at the clinicians' discretion (not determined in the study protocol) and according to a FDA analysis, about 20 % of patients did not receive first-line therapy at the time of myeloma diagnosis [9]. This might be a reflection of the fact that most cases of progression were due to biochemical rather than clinical markers. However, it is not known if the proportion of patients with immediate treatment was higher in the subgroup.

*Summary*

Time to diagnosis of myeloma was statistically significantly shorter in the active monitoring group than in the daratumumab group. However, most cases of progression were due to changes in biochemical, not clinical markers of disease. It is therefore difficult to interpret the significance of myeloma diagnosis for patients, especially as the data for time to first-line myeloma treatment cannot be interpreted with certainty. There are some indications that daratumumab may lead to a longer time before symptoms worsen. However, this is not shown consistently for all symptoms, and the magnitude might be marginally clinically relevant.

Table 11: GRADE assessment: Progression to myeloma

| Aspect | Down-grading | Certainty | Notes |
|---|---|---|---|
| Study type | | High | RCT |
| ROB | (↓) | | No downgrading for formal diagnosis, downgrading for symptoms due to progression (see Appendix 2) |
| Imprecision | ↓ | | Formal diagnosis: For the subgroup very large significant effect (HR 0.31), CI ratio of upper and lower boundaries <2. OIS according to the sample size calculations in the trial would require 165 events which is not met (24 + 56 events). Perceptible disease: Most CIs include the null effect. |
| Indirectness | (↓) | | No downgrading for formal diagnosis; downgrading for perceptible disease for patients |
| Inconsistency | ↓ | | Results are not consistent for all symptoms. |
| Publication bias | n.a. | | No concern |
| **Overall** | ↓(↓)(↓) | **Moderate**<br>**Very low** | **For subgroup results**<br>**for formal diagnosis**<br>**for perceptible disease** |
| RCT: randomised controlled trial; HR: hazard ratio; OIS: optimal information size; CI: confidence interval | | | |

*Conclusion for the decision aid*

- Less patients with daratumumab than with active monitoring may receive a diagnosis of myeloma. In the subgroup of high-risk according to Mayo 2018, 33 per 100 patients with daratumumab and 65 per 100 patients with active monitoring may receive a diagnosis of myeloma within five years. The certainty of the evidence is moderate. The DA should explain that these numbers refer to a trial in which most of the diagnoses were based on biochemical rather than clinical markers.
- Median time to diagnosis of active myeloma was 22 months in the subgroup high-risk according to Mayo 2018 in the active monitoring group. In the daratumumab group, the median time has not been reached with a follow-up time of approximately five years.
- It might take longer with daratumumab than with active monitoring until myeloma-related symptoms develop. However, this is not shown consistently for all symptoms, and the magnitude of the delay might be marginally clinically relevant. The certainty of the evidence is very low.

### FAQ 4: How will the treatment impact my quality of life?

HrQoL was assessed in the AQUILA trial via the respective domains of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). Additionally, results are available for the domain "future perspective" from the myeloma-specific questionnaire EORTC QLQ-MY20. In the IQWiG report, results from this instrument were not considered as not all domains were assessed in the trials ("body image" is missing).

The domains of HrQoL can be described as follows:

- Global health status refers to a general self-assessment of health status and quality of life.
- Physical function refers e.g. to the ability to carry a heavy shopping bag, taking a longer or shorter walk, need for rest during the day or need for help with eating, getting dressed or taking a shower.
- Role functioning refers to the ability to work, any limitations in everyday life, hobbies or leisure time activities.
- Emotional functioning refers to feeling stressed, depressed, worried, or irritable.
- Cognitive functioning refers to the ability to concentrate, e.g. reading the papers or watching television, or to remember certain things.
- Social functioning refers to any limitations in being together with other people, as family or friends.
- Future perspective refers to thinking about the illness and worrying about health in the future and dying.

In the AMNOG process, the minimal important ("relevant") difference has been defined as 10 points (10 %) for the respective items of EORTC QLQ-C30 and EORTC QLQ-MY20. This definition is adopted for this evidence report.

It should be noted that the follow-up for patient-reported efficacy outcomes was originally 18 months after progression and has been shortened in a later amendment to the study protocol to 6 months after progression. As there were more cases of progression in the active monitoring group, median follow-up was shorter than in the daratumumab group: about 51 months with daratumumab and about 38 months in the active monitoring group. Also, there were differences in the frequency of assessments according to progression status: Besides at the time of screening as well as end of study, patients answered the questionnaires in week 12, week 24, week 60 and once per year thereafter. In case of progression, there were additional questionnaires after progression. This might lead to detection bias with changes noted earlier in the treatment arm with more progression [5].

*Course of HrQoL*

During the trial, HrQoL did not change substantially from the baseline values for both groups and no statistically significant differences could be detected between the groups [8]. However, this might be partially attributable to the low frequency at which HrQoL was assessed during the trial. The FDA briefing therefore considers HrQoL data as not informative for the determination of the benefit-risk ratio [9].

*Delaying worsening of HrQoL*

When SMM progresses to active myeloma, with or without the development of symptoms, HrQoL might worsen.

The responder analyses for first relevant worsening of HrQoL can be found below (Table 12).

Table 12: First relevant worsening of health-related quality of life

| Domain | Population | Daratumumab<br>Proportion<br>Median time to event | Active monitoring<br>Proportion<br>Median time to event | Effect |
|---|---|---|---|---|
| Global health status | Full study population [6][a]<br>n = 390 | 56 per 100<br>29 months | 57 per 100<br>19 months | HR 0.76<br>(0.58; 0.99) |
| | Subgroup high risk Mayo 2018 [7][b]<br>n = 158 | 63 per 100<br>14 months | 52 per 100<br>15 months | HR 0.97<br>(0.64; 1.47) |
| Physical functioning | Full study population [6][a]<br>n = 390 | 53 per 100<br>42 months | 50 per 100<br>31 months | HR 0.83<br>(0.63; 1.10) |
| | Subgroup high risk Mayo 2018 [7][b]<br>n = 158 | 63 per 100<br>32 months | 55 per 100<br>18 months | HR 0.76<br>(0.50; 1.15) |
| Role functioning | Full study population [6][a]<br>n = 390 | 59 per 100<br>19 months | 56 per 100<br>20 months | HR 0.89<br>(0.68; 1.15) |
| | Subgroup high risk Mayo 2018 [7][b]<br>n = 158 | 65 per 100<br>14 months | 64 per 100<br>14 months | HR 0.77<br>(0.52; 1.13) |
| Emotional functioning | Full study population [6][a]<br>n = 390 | 47 per 100<br>54 months | 49 per 100<br>30 months | HR 0.69<br>(0.51; 0.92) |
| | Subgroup high risk Mayo 2018 [7][b]<br>n = 158 | 50 per 100<br>37 months | 47 per 100<br>28 months | HR 0.69<br>(0.44; 1.09) |
| Cognitive functioning | Full study population [6][a]<br>n = 390 | 47 per 100<br>51 months | 50 per 100<br>28 months | HR 0.77<br>(0.57; 1.02) |
| | Subgroup high risk Mayo 2018 [7][b]<br>n = 158 | 46 per 100<br>37 months | 50 per 100<br>24 months | HR 0.60<br>(0.38; 0.96) |

| | | | | |
|---|---|---|---|---|
| Social functioning | Full study population [6][a] n = 390 | 49 per 100 50 months | 47 per 100 39 months | HR 0.87 (0.65; 1.16) |
| | Subgroup high risk Mayo 2018 [7][b] n = 158 | 35 per 100 n.r. | 26 per 100 n.r. | HR 1.14 (0.64; 2.02) |
| Future perspective | Full study population [7][c] n = 390 | 50 per 100 47 months | 50 per 100 29 months | HR 0.80 (0.60; 1.06) |
| | Subgroup high risk Mayo 2018 [7][c] n = 158 | 53 per 100 30 months | 47 per 100 25 months | HR 0.85 (0.54; 1.33) |

Median follow-up: approximately 51 months with daratumumab, 38 months with active monitoring. For the assessment, the EORTC QLQ-C30 was used if not otherwise noted. Effect sizes are reported as point estimate and 95% confidence interval.
n.r. not reached; HR: hazard ratio.
[a] Table 15
[b] Appendix 4-H, Table 4-12, first relevant worsening
[c] Appendix 4-H, Table 4-14, first relevant worsening, EORTC QLQ-MY20

In the trial, about half of the patients experienced relevant worsening of HrQoL (with lower proportions only in the domain social functioning in the subgroup). For many domains, hazard ratios are quite similar for both the full study population and the subgroup. However, median time to first relevant worsening of HrQoL is consistently shorter for the subgroup with the exception of the domain social functioning. The proportions cannot be easily compared as the median follow-up differs between both treatment groups.

In the full study population, there is only a significant difference between the treatment arms for the domains global health status and emotional functioning. For the subgroup, the differences in these domains are not statistically significant, although the point estimate for emotional functioning is identical in both full study population. However, in the domain cognitive functioning, there is a statistically significant difference for the subgroup, but not for the full study population. The discrepancies regarding statistical significance might be due to lack of power for the subgroup. It is therefore reasonable to assume that there is some benefit, but not consistently in all domains.

The IQWiG report acknowledges an added benefit for daratumumab in the domains global health status and emotional functioning (based on the significant results for the full study population) which is clinically relevant. However, the magnitude is rated as minor.

If the significant difference for cognitive functioning would be assessed by the same criteria, the magnitude would also be clinically relevant, but minor.

Table 13: GRADE assessment: HrQoL

| Aspect | Down-/Upgrading | Certainty | Notes |
|---|---|---|---|
| Study type | | High | RCT |
| ROB | ↓ | | See Appendix 2 |
| Imprecision | ↓ | | Most CIs include the null effect |
| Indirectness | n.a. | | No concern |
| Inconsistency | ↓ | | Results are not consistent for all domains |
| Publication bias | n.a. | | No concern |
| **Overall** | ↓↓↓ | **Very low** | |
| RCT: randomised controlled trial; HR: hazard ratio; OIS: optimal information size; CI: confidence interval | | | |

*Conclusion for the decision aid*

- There is considerable uncertainty from the available data whether HrQoL is worse with daratumumab treatment than with active monitoring.
- There are some indications that daratumumab might better than active monitoring delay worsening of HrQoL. However, this is not consistent for all domains of HrQoL.
- The certainty of the evidence is very low.
- In the face of the uncertainty, the DA should not communicate effect sizes.

### FAQ 5: What are the short- or long-term risks or side effects?

Adverse events (AE) have been assessed in the AQUILA trial until 30 days after the last application of daratumumab or until the start of subsequent therapy in the daratumumab group and until 36 months after the start of the trial or until the start of subsequent therapy in the active monitoring group (whatever came first for both treatment arms). As the treatment duration differed between the groups, so did the follow-up time.

Very common adverse events (affected ≥ 20 % of patients), which occurred more frequently with daratumumab than with active monitoring (≥ 10 % difference), were fatigue, infections, diarrhoea, musculoskeletal pain (back pain, arthralgia), rash, sensory neuropathy and insomnia [9]. Selected operationalisations which were analysed in the early benefit assessment, can be found in Table 14.

For all operationalisations, proportions are higher with daratumumab than with active monitoring. Due to different lengths of follow-up, however, proportions are not easy to interpret.

Time to event for serious and severe adverse events in general was not significantly different between daratumumab and active monitoring, for both the full study population

and the subgroup. However, the confidence intervals are compatible with a substantial added risk for daratumumab (up to 2.5-fold). For severe infections, there is a higher risk with daratumumab than with active monitoring (about 4-fold for the point estimate and up to 10-fold in the upper limit of the confidence interval for the subgroup).

Table 14: Serious and severe adverse events

| Outcome | Population | Daratumumab<br><br>Proportion<br>Median time to event | Active monitoring<br>Proportion<br>Median time to event | Effect |
|---|---|---|---|---|
| Serious AE | Full study population [6][a]<br>n = 390 | 29 per 100<br>n.r. | 19 per 100<br>n.r. | HR 1.47<br>(0.97; 2.22) |
| | Subgroup high risk Mayo 2018 [7][b]<br>n = 158 | 37 per 100<br>37 months | 23 per 100<br>n.a. | HR 1.43<br>(0.79; 2.57) |
| Severe AE CTCAE grade ≥ 3 | Full study population [6][a]<br>n = 390 | 40 per 100<br>37 months | 31 per 100<br>n.r. | HR 1.33<br>(0.94; 1.86) |
| | Subgroup high risk Mayo 2018 [7][b]<br>n = 158 | 51 per 100<br>33 months | 31 per 100<br>33 months | HR 1.49<br>(0.90; 2.47) |
| Severe infections CTCAE grade ≥ 3 | Full study population [6][a]<br>n = 390 | 17 per 100<br>n.r. | 5 per 100<br>n.r. | HR 3.71<br>(1.74; 7.93) |
| | Subgroup high risk Mayo 2018 [7]c<br>n = 158 | 28 per 100<br>37 months | 7 per 100<br>n.r. | HR 3.83<br>(1.50; 9.75) |

Median follow-up: approximately 36 months with daratumumab, 27 months with active monitoring. Effect sizes are reported as point estimate and 95% confidence interval. n.r. not reached; HR: hazard ratio; RR: relative risk.

[a] Table 15

[b] Appendix 4-H, Table 4-16

[c] Appendix 4-H, Table 4-26

In the IQWiG report, the analyses for severe adverse events found an effect modification by sex for the full study population: more serious AE for men, but not for women [6].

For several specific adverse events, the IQWiG report acknowledges more harm for daratumumab in the full study population: gastrointestinal, neurological, dermatological, and vascular adverse events as well as general illness and reactions at the site of application, insomnia, severe infections, and ear and labyrinth disorders. For diseases of the respiratory tract, more harm with daratumumab was only found for women, not for men. Where more

harm was found, the magnitude was mostly considerable (2-4-fold), for severe infections even major [6].

Discontinuation due to adverse events occurred with 6 per 100 patients with daratumumab [8]. For this outcome, no subgroup analysis is available [7].

Despite pre- and post-administration medications, systemic injection-related reactions of any grade occurred in 17 per 100 patients with daratumumab. Grade 3 or 4 reactions occurred in 1 per 100 patients [8].

Table 15: GRADE assessment: Adverse events

| Aspect | Downgrading | Certainty | Notes |
|---|---|---|---|
| Study type | | High | RCT |
| ROB | ↓ | | See Appendix 2 |
| Imprecision | (↓↓) | | For serious and severe AE: CI includes the null effect, risk is only slightly increased, but CI includes important harm = downgrading twice<br><br>For serious infections: CI does not include the null, magnitude is major and so high that no downgrading is required<br><br>For other specific AE: CI does not include the null, magnitude is mostly considerable and so high that no downgrading is required |
| Indirectness | n.a. | | No concern |
| Inconsistency | n.a. | | No concern (single trial) |
| Publication bias | n.a. | | No concern |
| **Overall** | | **Moderate**<br><br>**Low** | **For severe infections and specific AE**<br><br>**For serious and severe AE in general** |

RCT: randomised controlled trial; HR: hazard ratio; CI: confidence interval; AE: adverse events; n.a.: no

*Conclusion for the decision aid*

- The DA should describe the most common AE as described above: fatigue, infections, diarrhoea, back pain, arthralgia rash, sensory neuropathy and insomnia.
- Side effects in general may be more common with daratumumab than with active monitoring (certainty of the evidence: moderate).
- Serious and severe AE in general might be similarly common with daratumumab compared to active monitoring; however, the certainty of the evidence is very low.
- The risk of severe infections can be communicated quantitatively using the results for the subgroup: The risk may be higher with daratumumab compared to active monitoring (certainty of the evidence: moderate). Within five years, 28 per 100 with daratumumab and 7 per 100 with active monitoring experience severe infections (at least one). The DA should point out that severe infections may require hospital treatment.
- In a trial, 6 per 100 patients within 5 years discontinued treatment due to AE. This might be added to the DA as supplementary information.
- Injection-related reactions affect approximately 17 per 100 patients, although severe reactions are less frequent (1 per 100 patients).

### FAQ 6: How do I know that the treatment works?

As the treatment aims to delay progression to active myeloma, patients experience successful treatment of SMM only via the absence of myeloma symptoms. However, as some of these symptoms are not specific (e.g. fatigue), they might occur in patients with SMM, although this condition is asymptomatic by definition.

There are regular check-ups (see FAQ 1) to detect progression to myeloma as early as possible.

### FAQ 7: How does the treatment impact my daily life?

Overall, there is not sufficient evidence for definitive conclusions about comparative HrQoL with both options.

Treatment with daratumumab requires more appointments at the doctor's office than active monitoring.

Due to the higher risk of infection with daratumumab, more precautions and medical treatment might be required to prevent and treat infections, including hospital treatment.

# DISCUSSION

## SUMMARY OF MAIN FINDINGS

This evidence report analysed data from the AQUILA trial [6–9] which compared treatment with daratumumab over a maximum of 3 years with active monitoring in patients with high-risk SMM.

There are some indications that treatment with daratumumab might lead to lower overall mortality compared to active monitoring, however, the certainty of the evidence is very low and especially not clear for the subgroup high-risk according to Mayo 2018 criteria. More patients received a diagnosis of active myeloma with active monitoring than with daratumumab (moderate certainty).

It is unclear whether treatment with daratumumab delays development of myeloma symptoms and worsening of HrQoL better than active monitoring (very low certainty for both outcomes).

There may be more severe infections and specific AE with daratumumab (moderate certainty), but the frequency of serious or other severe AE might be the same (low certainty).

Overall, patients might face a difficult choice: Early treatment with daratumumab might delay progression but comes with considerable side effects and treatment burden and might deprive them of a valuable first-line therapy option.

### *Comparison with the early benefit assessment*

Due to suboptimal subsequent therapy, the IQWiG report considered the data for overall survival as not interpretable [6]. We included the problem of suboptimal subsequent therapy in the GRADE assessment but also acknowledged the fact of a statistically significant difference between the treatment groups (full study population) and discussed the influence of the low number of events on the results for the high-risk (Mayo 2018) subgroup. The final G-BA rating also acknowledges the statistically significant differences in the context of relevant uncertainties due to the limited number of events and suboptimal subsequent therapy [14].

An indication for added benefit in delaying the worsening of symptoms and HrQoL was only acknowledged in some domains. The magnitude was rated as marginally clinically relevant for most symptoms and as clinically relevant for HrQoL in the IQWiG report [6]. We assessed the benefit of daratumumab as unclear for both outcomes, considering the FDA report which rated all patient-reported outcomes as not informative for the benefit-risk assessment due to sparse data [6]. The final G-BA rating included a moderate benefit for both morbidity and HrQoL [14].

The IQWiG report states an indication for considerable or major harm with daratumumab due to more severe infections and specific AE. However, there was no added harm in terms of serious AE or other severe AE [6]. In comparison, our assessment is similar for severe

infections and specific AE. For serious AE and other severe AE, we not only considered statistical significance, but also the upper border of the confidence interval for our assessment, leading to the rating that the certainty of the evidence for similar frequency is low. The final G-BA rating acknowledges neither relevant advantages nor relevant disadvantages of daratumumab in terms of adverse events [14].

Overall, the IQWiG report acknowledges indications for minor benefits which are outweighed by the harm, resulting in no added benefit [6]. In our assessment, we also included the outcome progression to myeloma (formal diagnosis) which indicates a benefit for daratumumab. In our assessment, however, we also discuss the open questions about the clinical relevance of this finding. Although we use a slightly different operationalisation, our result is similar to the final G-BA rating “indication of a minor added benefit” [14].

#### STRENGTH, LIMITATIONS AND UNCERTAINTIES

One strength of this evidence report is the extensive data base for the pivotal AQUILA trial. We did not rely on the journal publication [8] alone, but also added further data from the AMNOG dossier [7]. The interpretation of the data was enhanced by insights from an IQWiG report [6] and a FDA report [9].

However, there are several limitations of the evidence:

- The inclusion criteria of the AQUILA trial were much broader than the target group for the DA. Therefore, we relied, wherever possible, on a subgroup analysis of patients which were classified as high-risk according to Mayo 2018 criteria. However, as this group was only about 40 % of the full study population, all analyses lack power.
- The interpretation of overall mortality data is hampered by suboptimal subsequent therapy, leading to a very low certainty.
- The data on progression mainly relies on biochemical than clinical markers. However, biochemical criteria have been added to the diagnostic criteria of myeloma over a decade ago [2], as they are prognostic for end organ damage within few years.
- The significance of the diagnosis for patients cannot be easily explored with the trial data as patient-reported data have been only sparsely assessed.
- Although more patients progressed with active monitoring, about a third of the high-risk patients progressed despite treatment. Also, a third of patients with active monitoring had no progression within five years. In clinical practice, it will be challenging to identify patients with high-risk SMM who might benefit from daratumumab treatment.
- There is no sufficient data from the AQUILA trial or other trials to assess the impact for the further course of the disease when patients progress to active myeloma

while on treatment with daratumumab. In this case, patients will be classified as CD38 refractory and effective quadruplets will be no option for first-line therapy.

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## APPENDIX 1: SEARCH AND RETRIEVAL OF THE EVIDENCE

### Guidelines

*Search strategy*

| Source | Search date | Search term | Filters or exclusion criteria | Retrieval |
|---|---|---|---|---|
| GIN International Guidelines Library https://guidelines.ebmportal.com/ | 24.10.2025 | myeloma | Filters: 2021-2025; status: published | 1 |
| Website International Myeloma Working Group (IMWG) https://www.myeloma.org/imwg-publications | 24.10.2025 | n.a. (hand-searching) | Excluded: Guidelines for relapsed/refractory multiple myeloma only | 0 |
| Website European Society For Medical Oncology (ESMO) https://www.esmo.org/guidelines/esmo-clinical-practice-guidelines-haematological-malignancies | 24.10.2025 | n.a. (hand-searching) | Excluded: Guidelines for relapsed/refractory multiple myeloma only | 1 |
| Website European Hematology Association (EHA) https://ehaweb.org/clinical-practice/guidelines-by-areas-of-disease | 24.10.2025 | n.a. (hand-searching) | Excluded: Guidelines for relapsed/refractory multiple myeloma only | 1 |

*Full text screening*

| Publisher (Year) | Link | Suitable for data extraction?[a] | Decision |
|---|---|---|---|
| ESMO (2021) | https://www.annalsofoncology.org/article/S0923-7534(20)43169-2/fulltext | No: Probably no systematic search, no detailed data to inform the FAQs. | Excluded |
| AWMF/OL (2022) | https://www.leitlinienprogramm-onkologie.de/leitlinien/multiples-myelom | No: Systematic search, but too old (2018). | Excluded |
| EHA-EMN (2025) | https://www.nature.com/articles/s41571-025-01041-x | No: Unclear if a systematic search has been conducted. No detailed data to inform the FAQs. | Excluded |

### HTA reports

*Search strategy*

| Source | Search date | Search term | Filters or exclusion criteria | Retrieval |
|---|---|---|---|---|
| INAHTA database<br>https://database.inahta.org/ | 27.10.2025 | "Smoldering Multiple Myeloma"[mh] | n.a. | No hits |
| IQWiG website<br>https://iqwig.de/projekte/projekte-und-ergebnisse | 17.11.2025 | Hand searching | Newer HTA reports on daratumumab or isatuximab not yet in the INAHTA database | 1, included |

**RCTs**

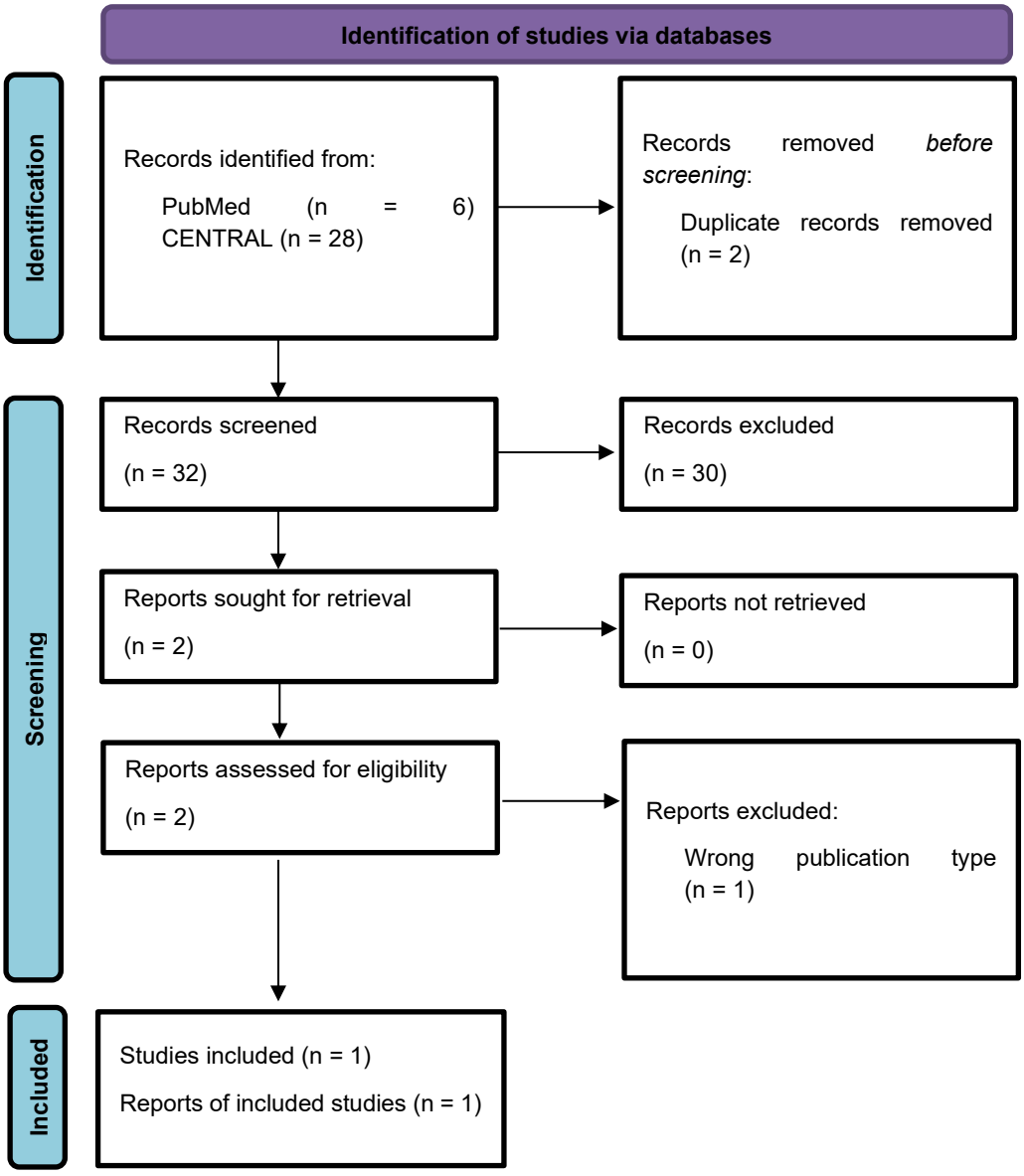
*Search strategy*

| Source and search date | Search term | Filters or exclusion criteria | Retrieval |
|---|---|---|---|
| PubMed<br>19.11.2025 | #1: "smoldering multiple myeloma"[MeSH Terms] OR (("smoldering"[Title/Abstract] OR "smouldering"[Title/Abstract]) AND "myelom*"[Title/Abstract]<br>#2: "daratumumab*"[Title/Abstract] OR "darzalex*"[Title/Abstract] OR "CD38"[Title/Abstract] OR "anti-CD38"[Title/Abstract] OR "CD 38"[Title/Abstract]<br>#3: #1 AND #2 = 74 Treffer<br>#4: "randomized controlled trial"[Publication Type] OR "random*"[Title/Abstract]<br>#5: #3 AND #4 | n.a. | 6 |
| Cochrane Library<br>19.11.2025 | #1: MeSH descriptor: [Smoldering Multiple Myeloma] explode all trees<br>#2: ((smoldering OR smouldering) AND myelom*):ti,ab<br>#3: #1 OR #2<br>#4: (daratumumab* OR darzalex* OR CD38 OR anti-CD38 OR “CD 38”):ti,ab<br>5: #3 AND #4 | EMBASE | 29 |

*Full text screening*

**Dimopoulos 2025** https://pubmed.ncbi.nlm.nih.gov/39652675/
AQUILA, included

**Mohyuddin 2025** https://pubmed.ncbi.nlm.nih.gov/40674588/
narrative review/commentary, excluded



## APPENDIX 2: RISK OF BIAS ASSESSMENT

| Outcome | Rating | Notes |
|---|---|---|
| Overall survival | High | Due to insufficient second-line therapy |
| Progression | Low | Progression is assessed by a validated computer algorithm according to pre-defined and well-established criteria. |
| PRO: symptoms, quality of life | High [a] | Due to unblinded outcome assessment for subjective outcomes; incomplete follow-up and differing follow-up duration for the trial arms |
| Adverse events | High [a] | incomplete follow-up and differing follow-up duration for the trial arms; for non-serious/severe AE additionally due to unblinded outcome assessment for subjective outcomes |
| The risk of bias (RoB) assessment relies on the IQWiG report [6] and own judgement (see Notes) for the outcomes where no ratings are available. RoB on the study-level has been assessed as low in the IQWiG report.<br>[a] Rating directly adopted from IQWiG report, Table 14 | | |