Daratumumab (systemic light-chain amyloidosis)

Benefit assessment according to §35a SGB V[1] (Expiry of the decision)

EXTRACT

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Medical and scientific advice

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

Patient and family involvement

The questionnaire on the disease and its treatment was answered by one person.

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

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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
AL amyloidosis	light chain amyloidosis
ASCT	autologous stem cell transplantation
CHR	complete haematological response
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group - Performance Status
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MCS	Physical Component Summary
MOD-PFS	Major Organ Deterioration-Progression Free Survival
NYHA	New York Heart Association
PCS	Physical Component Summary
PR	partial response
QLQ-MY20	EORTC Quality of Life Questionnaire-Multiple Myeloma Module 20
QLQ-OV28	EORTC Quality of Life Questionnaire-Ovarian Cancer Module 28
QLQ-PR25	EORTC Quality of Life Questionnaire-Prostate 25
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	Summary of Product Characteristics
VCd	cyclophosphamide, bortezomib and dexamethasone
VGPR	very good partial response

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug daratumumab in combination with cyclophosphamide, bortezomib and dexamethasone (VCd). The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 28 February 2025.

The company had already submitted a dossier for a previous benefit assessment of the drug to be assessed. The dossier was sent to IQWiG on 27 July 2021. In that procedure, by resolution of 20 January 2022, the G-BA limited the period of validity of the resolution to 1 March 2025. In the earlier benefit assessment procedure, an added benefit was only determined for adult patients with newly diagnosed systemic AL amyloidosis for whom VCd is the suitable therapy for the individual patient. The present assessment refers exclusively to this patient population, which was defined in the earlier benefit assessment procedure. The time limit is based on the fact that the analyses on overall survival presented by the company from the ANDROMEDA study were not very informative due to the low number of events for the data cut-off used. For the renewed benefit assessment after the deadline, the dossier should include the expected results of the final analyses on overall survival as well as, in particular, the results on the outcome major organ deterioration and on all further patient-relevant outcomes from the ANDROMEDA study which are used to demonstrate an added benefit.

Research question

The aim of this report is to assess the added benefit of daratumumab in combination with VCd compared with VCd as an appropriate comparator therapy (ACT) in adults with newly diagnosed systemic light-chain amyloidosis (AL amyloidosis) for whom VCd is the suitable therapy for the individual patient.

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

Table 2: Research questions of the benefit assessment of daratumumab + VCd

Therapeutic indication	**ACT[a]**
Adults with newly diagnosed systemic AL amyloidosis for whom bortezomib in combination with cyclophosphamide and dexamethasone is the suitable therapy for the individual patient[b]	Bortezomib in combination with cyclophosphamide and dexamethasone[c] (VCd)

a. Presented is the ACT specified by the G-BA.
b. This research question arises in contrast to other options of individualized treatment for newly diagnosed systemic AL amyloidosis (see dossier assessment A21-100). Apart from daratumumab in combination with VCd, no drug therapies are approved for the treatment of AL amyloidosis. As part of a clinical study in A21-100, various therapy combinations were considered suitable comparators for patient-specific therapy, including VCd. The ACT also included high-dose melphalan therapy with subsequent autologous stem cell transplantation (ASCT) as part of an individualized treatment for suitable patients. This could be indicated immediately or after completed induction therapy. In principle, the therapeutic indication also covers patients for whom immediate ASCT is an option.
c. Apart from daratumumab in combination with VCd, no other drugs are approved for this indication. According to Section 6 (2) sentence 2 of the Regulation on the Benefit Assessment of Drugs (AM-NutzenV), the determination of the ACT in this context is to be based on the actual health care situation as it would be without the drug to be assessed. The G-BA points out that the use of VCd is medically necessary. According to the generally recognized state of medical knowledge with regard to the patient group to be assessed, off-label use is considered the therapy standard.

ASCT: autologous stem cell transplantation; AL amyloidosis: light-chain amyloidosis; AM-NutzenV: Regulation for Early Benefit Assessment of New Pharmaceuticals; G-BA: Federal Joint Committee; VCd: bortezomib + cyclophosphamide + dexamethasone

The company initially formulated the research question analogously to the research question of the initial assessment (A21-100). In doing so, the company named adult patients with newly diagnosed systemic AL amyloidosis as the patient population. For this patient population, the ACT corresponds to the individualized treatment defined in the initial assessment, taking into account general condition, comorbidities and organ damage. In the following, however, the company restricted the patient population to adults with newly diagnosed systemic AL amyloidosis for whom VCd is the suitable therapy for the individual patient. This corresponds to the patient population defined by the G-BA for the time limit and is therefore appropriate.

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 ANDROMEDA study was used for the benefit assessment. ANDROMEDA is an open-label RCT comparing daratumumab + VCD with VCd. The study included adults with newly diagnosed systemic AL amyloidosis. In addition to a histopathologic diagnosis, a measurable disease had to be present, defined by exceeding defined threshold values of serum M-protein and/or free light chains in the serum. Patients should have at least 1 organ affected by AL

amyloidosis and an Eastern Cooperative Oncology Group - Performance Status (ECOG PS) ≤ 2. Patients with abnormal cardiovascular conditions such as New York Heart Association (NYHA) stage IIIb or IV heart failure and a planned autologous stem cell transplantation (ASCT) within the first 6 cycles of treatment were excluded from participation in the study.

The study included a total of 388 patients, randomly allocated in a 1:1 ratio to the treatment arms daratumumab + VCd (N = 195) or VCd (N = 193).

The study medication was administered in 28-day cycles in both treatment arms. Patients in the intervention arm received daratumumab + VCd in the first 6 cycles and daratumumab as monotherapy from Cycle 7 to a maximum of 24 cycles. Patients in the comparator arm received a maximum of 6 cycles of VCd. Daratumumab + VCd was administered subcutaneously and in compliance with the Summary of Product Characteristics (SmPC). Treatment with VCd in the comparator arm was carried out in accordance with the administration of VCd in the intervention arm. Patients were treated until disease progression, start of subsequent therapy, unacceptable toxicity or withdrawal of consent.

The study's primary outcome is the complete haematological response (CHR). Patient-relevant secondary outcomes are overall survival, outcomes on morbidity as well as health-related quality of life and adverse events (AEs).

Data cut-offs

In Module 4 A, the company used the results of the second data cut-off (17 April 2024) for the benefit assessment. For the outcomes overall survival and AEs, it also presents the results for the final data cut-off (15 November 2024). For the outcomes in the categories morbidity and health-related quality of life, analyses are therefore not available for all relevant outcomes for the relevant final data cut-off (15 November 2024) of the ANDROMEDA study. As the recording of the AE outcomes was linked to the treatment duration, these were no longer recorded after the second data cut-off (17 April 2024). Accordingly, the results of the second data cut-off and the final data cut-off are identical. In this benefit assessment, the final data cut-off (15 November 2024) is used for the outcomes in the categories mortality and side effects. After the second data cut-off (17 April 2024), no further recordings were conducted for the outcome major organ deterioration. Furthermore, the additional surveys of patient-reported outcomes in the final data cut-off (15 November 2024) compared to the second data cut-off (17 April 2024) and their influence on the results are estimated to be very minor. Therefore, the second data cut-off (17 April 2024) was used for the outcomes in the categories morbidity and health-related quality of life.

Suitability of the patient population included in the ANDROMEDA study for this research question

In the previous benefit assessment procedure, an individualized treatment was defined as ACT for adults with newly diagnosed systemic AL amyloidosis, taking into account general condition, comorbidities and organ damage. The following therapies, all of which are not approved, were considered suitable comparators: bortezomib + cyclophosphamide + dexamethasone, bortezomib ± dexamethasone, bortezomib + melphalan + dexamethasone, lenalidomide + cyclophosphamide + dexamethasone, lenalidomide + dexamethasone, melphalan + dexamethasone, lenalidomide + melphalan + dexamethasone, high-dose melphalan therapy followed by ASCT (immediately or after completed induction). Based on the ANDROMEDA study, statements on the added benefit of daratumumab + VCd compared to individualized treatment under consideration of the general condition, comorbidities and organ damage, could only be derived for the subpopulation of those patients for whom VCd is the suitable therapy for the individual patient. The G-BA specified a time limit of the validity of its decision exclusively for these patients.

The research question of this benefit assessment thus only comprises adult patients with newly diagnosed systemic AL amyloidosis for whom VCd is the suitable therapy for the individual patient (see Table 2). At the time of the current assessment, VCd and daratumumab + VCd are the most suitable therapies for the majority of patients included in the study. However, it is uncertain whether treatment with VCd is the most suitable therapy for all patients in the ANDROMEDA study. For these patients, it is unclear how many would have been immediately eligible (or in the later course following induction therapy) for high-dose melphalan therapy followed by ASCT as an individualized treatment. The certainty of conclusions is therefore reduced for all outcomes.

Risk of bias and certainty of conclusions

The risk of bias across outcomes for the results of the ANDROMEDA study was rated as low. At outcome level, the risk of bias of the results was rated as high for all outcomes except “overall survival”. Due to the reduced certainty of conclusions entailed by the uncertainty regarding the suitability of the patient population included in the ANDROMEDA study, at most hints, e.g. of added benefit, can be derived for the present research question for all outcomes on the basis of the effects shown in the ANDROMEDA study.

Results

Mortality

Overall survival

The final data cut-off (15 November 2024) showed a statistically significant difference in favour of daratumumab + VCd for the outcome overall survival. There is thus a hint of an added benefit of daratumumab + VCd over VCd.

Morbidity

Major organ deterioration

For the composite outcome major organ deterioration, consisting of clinical manifestation of heart failure and clinical manifestation of renal failure, there is a statistically significant difference in favour of daratumumab + VCd at the second data cut-off of 17 April 2024. The results are particularly influenced by the component clinical manifestation of renal failure. There is thus a hint of an added benefit of daratumumab + VCd over VCd.

Symptoms

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and EORTC QLQ indivdual items

Dyspnoea

For the outcome dyspnoea (recorded with the EORTC QLQ-C30), there was a statistically significant difference in favour of daratumumab + VCd in the analysis of the time to first deterioration at the second data cut-off of 17 April 2024. However, the extent of the effect is no more than marginal for this outcome. There is no hint of an added benefit of daratumumab + VCd in comparison with VCd; an added benefit is therefore not proven.

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

For each of the outcomes fatigue, nausea and vomiting, pain, insomnia, appetite loss, constipation and diarrhoea (recorded using the EORTC QLQ-C30), there was no statistically significant difference between the treatment groups in the analysis of the time to first deterioration at the second data cut-off of 17 April 2024. In each case, there was no hint of an added benefit of daratumumab + VCd in comparison with VCd; an added benefit is therefore not proven.

Tingling in the hands and feet (EORTC Quality of Life Questionnaire-Multiple Myeloma Module 20 [QLQ-MY20]), feeling of fullness in the abdomen/stomach (EORTC Quality of Life Questionnaire-Ovarian Cancer Module 28 [QLQ-OV28]) and swelling of the legs or ankles (EORTC Quality of Life Questionnaire-Prostate 25 [QLQ-PR25])

For each of the outcomes tingling in the hands and feet (EORTC QLQ-MY20), feeling of fullness in the abdomen/stomach (EORTC QLQ-OV28) and swelling of the legs or ankles (EORTC QLQ-

PR25), there was no statistically significant difference between the treatment groups in the analysis of the time to first deterioration at the second data cut-off of 17 April 2024. In each case, there was no hint of an added benefit of daratumumab + VCd in comparison with VCd; an added benefit is therefore not proven.

Health status

For health status (recorded using the EQ-5D VAS), there was no statistically significant difference between the treatment groups in the analysis of the time to first deterioration at the second data cut-off of 17 April 2024. There is no hint of an added benefit of daratumumab + VCd in comparison with VCd; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

Global health status, physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning

For the outcomes global health status, physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning (recorded using the EORTC QLQ-C30), there was no statistically significant difference between the treatment groups in the analysis of the time to first deterioration at the second data cut-off of 17 April 2024. In each case, there was no hint of an added benefit of daratumumab + VCd in comparison with VCd; an added benefit is therefore not proven.

SF-36

For the Physical Component Summary (PCS) and the Mental Component Summary (MCS), measured using the SF-36, the analysis of the time to first deterioration showed no statistically significant difference between the treatment arms at the second data cut-off of 17 April 2024. In each case, there was no hint of an added benefit of daratumumab + VCd in comparison with VCd; an added benefit is therefore not proven.

Side effects

SAEs, severe AEs, and discontinuation due to AEs

There was no statistically significant difference between the treatment arms for the outcomes SAEs, severe AEs and discontinuation due to AEs at the final data cut-off of 15 November 2024. There is no hint of greater or lesser harm from daratumumab + VCd in comparison with VCd; greater or lesser harm is therefore not proven.

Peripheral neuropathy (AEs)

There was no statistically significant difference between the treatment arms for the outcome peripheral neuropathy (AE) at the final data cut-off of 15 November 2024. There is no hint of

greater or lesser harm from daratumumab + VCd in comparison with VCd; greater or lesser harm is therefore not proven.

Skin and subcutaneous tissue disorders (AEs)

The final data cut-off of 15 November 2024 showed a statistically significant difference to the disadvantage of daratumumab + VCd for the outcome skin and subcutaneous tissue disorders (AEs). There is a hint of greater harm from daratumumab + VCd in comparison with VCd.

Hypokalaemia (severe AEs)

The final data cut-off of 15 November 2024 showed a statistically significant difference in favour of daratumumab + VCd for the outcome hypokalaemia (severe AEs). There is a hint of lesser harm from daratumumab + VCd in comparison with VCd.

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

On the basis of the results presented, the probability and the extent of the added benefit of the drug daratumumab + VCd compared with the ACT is assessed as follows:

All things considered, both positive and negative effects of different extents were found for daratumumab + VCd compared with VCd.

On the positive effects side, there is a hint of considerable added benefit for the outcome overall survival and for the category of severe/serious symptoms. Moreover, there was a hint of lesser harm with the extent "minor" in the category of serious/severe side effects. In the category non-serious/non-severe side effects there is a hint of greater harm with the extent "considerable". The negative effect with considerable extent in the outcome category of non-serious/non-serious side effects does not challenge the positive effects.

In summary, for patients with newly diagnosed systemic AL amyloidosis for whom VCd is the appropriate therapy for the individual patient, there is a hint of a considerable added benefit of daratumumab + VCd compared with the ACT VCd.

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

Table 3 presents a summary of the probability and extent of added benefit of daratumumab + VCd in comparison with the ACT.

Table 3: Daratumumab + VCd – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with newly diagnosed systemic AL amyloidosis for whom bortezomib in combination with cyclophosphamide and dexamethasone is the suitable therapy for the individual patient[b]	Bortezomib in combination with cyclophosphamide and dexamethasone[c] (VCd)	Hint of considerable added benefit

a. Presented is the ACT specified by the G-BA.
b. This research question arises in contrast to other options of individualized treatment for newly diagnosed systemic AL amyloidosis (see dossier assessment A21-100). Apart from daratumumab in combination with VCd, no drug therapies are approved for the treatment of AL amyloidosis. As part of a clinical study in A21-100, various therapy combinations were considered suitable comparators for patient-specific therapy, including VCd. The ACT also included high-dose melphalan therapy with subsequent ASCT as part of an individualized treatment for suitable patients. This could be indicated immediately or after completed induction therapy. In principle, the therapeutic indication also covers patients for whom immediate ASCT is an option.
c. Apart from daratumumab in combination with VCd, no other drugs are approved for this indication. According to Section 6 (2) sentence 2 of the Regulation on the AM-NutzenV, the determination of the ACT in this context is to be based on the actual health care situation as it would be without the drug to be assessed. The G-BA points out that the use of VCd is medically necessary. According to the generally recognized state of medical knowledge with regard to the patient group to be assessed, off-label use is considered the therapy standard.

ASCT: autologous stem cell transplantation; AL amyloidosis: light-chain amyloidosis; AM-NutzenV: Regulation for Early Benefit Assessment of New Pharmaceuticals; G-BA: Federal Joint Committee; VCd: bortezomib + cyclophosphamide + dexamethasone

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

I 2 Research question

The aim of this report is to assess the added benefit of daratumumab in combination with VCd compared with VCd as ACT in adults with newly diagnosed AL amyloidosis for whom VCd is the suitable therapy for the individual patient.

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

Table 4: Research questions of the benefit assessment of daratumumab + VCd

Therapeutic indication	**ACT**[a]
Adults with newly diagnosed systemic AL amyloidosis for whom VCd is the suitable therapy for the individual patient[b]	VCd[c]

a. Presented is the ACT specified by the G-BA.
b. This research question arises in differentiation from other options of individualized treatment for newly diagnosed systemic AL amyloidosis (see dossier assessment A21-100 [3]). Apart from daratumumab in combination with VCd, no drug therapies are approved for the treatment of AL amyloidosis. In A21-100, various therapy combinations were considered suitable comparators for individualized therapy, including VCd, as part of a clinical study. The ACT also included high-dose melphalan therapy with subsequent ASCT as part of an individualized treatment for suitable patients. This could be indicated immediately or after completed induction therapy. In principle, the therapeutic indication also covers patients for whom immediate ASCT is an option.
c. Apart from daratumumab in combination with VCd, no other drugs are approved for this indication. According to Section 6 (2) sentence 2 of the Regulation on the AM-NutzenV, the determination of the ACT in this context is to be based on the actual health care situation as it would be without the drug to be assessed. The G-BA points out that the use of VCd is medically necessary. According to the generally recognized state of medical knowledge with regard to the patient group to be assessed, off-label use is considered the therapy standard.

ASCT: autologous stem cell transplantation; AL amyloidosis: light-chain amyloidosis; AM-NutzenV: Regulation for Early Benefit Assessment of New Pharmaceuticals; G-BA: Federal Joint Committee; VCd: bortezomib + cyclophosphamide + dexamethasone

The company initially formulated the research question analogously to the research question of the initial assessment (A21-100) [3]. In doing so, the company named adult patients with newly diagnosed systemic AL amyloidosis as the patient population. For this patient population, the ACT corresponds to the individualized treatment defined in the initial assessment, taking into account general condition, comorbidities and organ damage. In the following, however, the company restricted the patient population to adults with newly diagnosed systemic AL amyloidosis for whom VCd is the suitable therapy for the individual patient. This corresponds to the patient population defined by the G-BA for the time limit and is therefore appropriate.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used to derive the added benefit. This concurs 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: 04 December 2024)
- bibliographical literature search on daratumumab (last search on 4 December 2024)
- search in trial registries/study results databases on daratumumab (last search on 12 December 2024)
- search on the G-BA website on daratumumab (last search on 4 December 2024)

To check the completeness of the study pool:

- search in trial registries for studies on daratumumab (last search on 14 March 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 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: daratumumab + VCd compared with VCd

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])
54767414AMY3001 (ANDROMEDA[c])	Yes	Yes	No	Yes [4,5]	Yes [6-8]	Yes [9-13]

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.
RCT: randomized controlled trial; VCd: bortezomib + cyclophosphamide + dexamethasone

The study pool of this benefit assessment comprises the RCT ANDROMEDA and corresponds to the study pool of the company.

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 + VCd compared with VCd (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study implementation	Primary outcome; secondary outcomes[a]
ANDROMEDA	RCT[b], open-label, parallel	Adults (≥ 18 years) with newly diagnosed AL amyloidosis[c] ▪ ≥ 1 organ affected by AL-amyloidosis[d] ▪ without conspicuous cardiovascular conditions[e] ▪ without planned ASCT within the first 6 cycles of treatment ▪ ECOG PS ≤ 2	Daratumumab + VCd (N = 195) VCd (N = 193)	Screening: 28 days treatment: ▪ daratumumab: at most 24 cycles ▪ VCd (in both study arms): at most 6 cycles or until disease progression, start of subsequent therapy, unacceptable toxicity or withdrawal of consent observation: outcome-specific[f], at most until death or end of study[g]	140 centres in Australia, Belgium, Brazil, Canada, China, Denmark, France, Germany, Greece, Hungary, Israel, Italy, Japan, Mexico, Netherlands, Poland, South Korea, Spain, Sweden, Turkey, United Kingdom, USA 10/2017–11/2024 data cut-offs[h]: 14 February 2020[i] 17 April 2024[j] 15 November 2024[k]	Primary: overall CHR rate secondary: overall survival, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: daratumumab + VCd compared with VCd (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study implementation	Primary outcome; secondary outcomes[a]

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. Prior to randomization, a single-arm run-in phase was conducted to assess the safety profile of daratumumab + VCd.
c. Proven by a histopathological diagnosis and a measurable disease:
- histological diagnosis: amyloid detection by immunohistochemistry and green birefringence in the polarization microscope of tissue samples from organs other than the bone marrow, which have previously been stained with Congo red, or by a characteristic appearance in the electron microscope. Mass spectrometric typing of an AL amyloid in a tissue biopsy is recommended for male study participants ≥ 70 years of age who have only cardiac involvement, and for study participants of African family origin.
- measurable disease defined by ≥ 1 of the following criteria: serum M protein ≥ 0.5 g/dL by protein electrophoresis (routine serum protein electrophoresis and immunofixation electrophoresis determined in a central laboratory) and/or free light chains in serum ≥ 50 mg/L with abnormal kappa-lambda ratio or a difference between involved and uninvolved free light chains (dFLC) ≥ 50 mg/L

d. Definition of organ involvement according to NCCN Guideline Systemic Light Chain Amyloidosis [14]
e. N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) > 8500 ng/L, NYHA stage IIIb or IV heart failure, heart failure which the investigator considers to be based on ischaemic heart disease or uncorrected valvular heart disease and which is not primarily due to amyloid cardiomyopathy, hospitalization for unstable angina pectoris or myocardial infarction within the 6 months prior to the first medication or percutaneous coronary intervention with new stent or coronary artery bypass grafting within 6 months; in case of heart failure: cardiovascular-related hospitalization ≤ 4 weeks prior to randomization, history of persistent ventricular tachycardia or terminated ventricular fibrillation, history of AV or SA node dysfunction for which a pacemaker or implantable cardioverter/defibrillator was indicated but not used; at screening: 12-lead ECG showing a QTcF > 500 ms at baseline, supine systolic blood pressure < 90 mm Hg, or symptomatic orthostatic hypotension, defined as a decrease in systolic blood pressure while standing of > 20 mm Hg despite drug treatment.
f. Outcome-specific information is provided in Table 8.
g. Five years after randomization of the last patient.
h. On 15 June 2020, an additional data cut-off was made as part of a safety update required by the FDA 4 months after the first data cut-off.
i. Prespecified data cut-off, planned after the last patient had been treated for 6 months.
j. Prespecified data cut-off, planned after 200 MOD-PFS events have occurred.
k. Prespecified final data cut-off, planned 5 years after inclusion of the last patient.

Table 6: Characteristics of the study included – RCT, direct comparison: daratumumab + VCd compared with VCd (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study implementation	Primary outcome; secondary outcomes[a]
AE: adverse event; AL amyloidosis: light-chain amyloidosis; ASCT: autologous stem cell transplantation; AV: atrioventricular; CHR: complete haematological response; ECOG PS: Eastern Cooperative Oncology Group - Performance Status; ECG: electrocardiogram; FDA: Food and Drug Administration; Hg: mercury; MOD-PFS: Major Organ Deterioration-Progression Free Survival; N: number of randomized patients; NCCN: National Comprehensive Cancer Network; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; QT: number of randomized patients; NCCN: National Cancer Control Network; NT-proBNP: N-terminal pro-brain natriuretic peptide; N-terminal pro-brain natriuretic peptide: number of randomized patients; NCCN: National Comprehensive Cancer Network; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; QTcF: corrected QT interval (Fridericia); RCT: randomized controlled trial; SA: sinuatrial; VCd: bortezomib + cyclophosphamide + dexamethasone						

Table 7: Characteristics of the intervention – RCT, direct comparison: daratumumab + VCd compared with VCd (multipage table)

Study	Intervention	Comparison
ANDROMEDA	Daratumumab 1800 mg, SC ▪ Cycles 1–2: weekly (Days 1, 8, 15 and 22) ▪ Cycles 3–6: every 2 weeks (Days 1 and 15) ▪ from Cycle 7: every 4 weeks (Day 1) + bortezomib 1.3 mg/m^2 BSA, SC[a] ▪ Cycles 1–6: weekly (Days 1, 8, 15 and 22) + cyclophosphamide 300 mg/m^2 BSA[b], orally or IV ▪ Cycles 1–6: weekly (Days 1, 8, 15 and 22) + dexamethasone[c] 40 mg[d, e], IV or orally ▪ Cycles 1–6: weekly (Days 1, 8, 15 and 22) duration of cycle: 28 days	 bortezomib 1.3 mg/m^2 BSA, SC[a] ▪ Cycles 1–6: weekly (Days 1, 8, 15 and 22) + cyclophosphamide 300 mg/m^2 BSA[b], orally or IV ▪ Cycles 1–6: weekly (Days 1, 8, 15 and 22) + dexamethasone[c] 40 mg[d, e], IV or orally ▪ Cycles 1–6: weekly (Days 1, 8, 15 and 22) duration of cycle: 28 days
	Dose adjustment/treatment interruptions ▪ daratumumab: no dose adjustment allowed; treatment interruptions due to toxicity permitted for up to 28 days in Cycles 1-6 and up to 6 weeks from Cycle 7 onwards ▪ bortezomib: 2 dose reductions due to toxicity allowed (first reduction to 1.0 mg/m^2 BSA, second reduction to 0.7 mg/m^2 BSA); treatment interruptions due to non-haematological toxicity (grade 3), haematological toxicity (grade 4) or peripheral neuropathies (grade 2 with pain or grade 3)[f] ▪ cyclophosphamide: dose reduction by 50% for neutrophil count 1500-1000/mm^3 and/or platelet count 50 000-100 000/µL, treatment interruption for neutrophil count < 1000/mm^3 and/or platelet count < 50 000/µl ▪ dexamethasone: dose reductions allowed at the investigator's discretion	
	Premedication before daratumumab ▪ 1-3 hours before administration of daratumumab: paracetamol (650-1000 mg, orally or IV), antihistamine (25-50 mg diphenhydramine or equivalent), dexamethasone[c] (20 mg, orally or IV) ▪ optional in Cycle 1 on Day 1 up to 24 hours before administration of daratumumab: montelukast (10 mg, oral) or equivalent **postmedication after daratumumab** ▪ to be considered the day after administration of daratumumab: low-dose oral methylprednisolone (≤ 20 mg) or equivalent[g] ▪ for patients with a higher risk of respiratory complications, the following drugs should be considered after the infusion: antihistamines (diphenhydramine or equivalent), leukotriene inhibitors (montelukast or equivalent), short-acting beta-2 sympathomimetics, control medications for the respective lung disease (e. g. inhaled corticosteroids)	

Table 7: Characteristics of the intervention – RCT, direct comparison: daratumumab + VCd compared with VCd (multipage table)

Study	Intervention	Comparison
	Disallowed pretreatment ▪ any therapies for the treatment of AL amyloidosis or multiple myeloma, including drugs that target CD38[h] ▪ strong CYP3A4 inducers < 5 half-lives before the first dose of the study medication **concomitant treatment** **recommended** ▪ infection prophylaxis (pneumocystis pneumonia prophylaxis, herpes zoster prophylaxis, hepatitis B prophylaxis) ▪ prophylaxis and treatment of haemorrhagic cystitis ▪ management of peripheral and pulmonary oedema and heart failure **not allowed during the first 6 cycles** ▪ other therapies for the treatment of AL amyloidosis, including drugs that target CD38 ▪ additional administration of corticosteroids[i] ▪ other investigational preparations ▪ strong CYP3A4 inducers when bortezomib is administered	

a. In the case of injection-related side effects, bortezomib could also be administered as an infusion.
b. At most 500 mg/week regardless of body surface area.
c. Substitution by an equivalent drug in accordance with local standards possible.
d. In the intervention arm on days without daratumumab administration and in the comparator arm: 40 mg on 1 day or distributed over 2 days; on days with daratumumab administration in the intervention arm: 20 mg as premedication for daratumumab + 20 mg on the day after daratumumab administration.
e. For patients over 70 years of age, BMI < 18.5, hypovolaemia, poorly controlled diabetes mellitus or in case of intolerances/AEs in connection with steroid therapy in the past, a dosage of 20 mg was possible (in the intervention arm on the days with daratumumab administration as premedication).
f. After treatment interruption due to peripheral neuropathy, the dose is adjusted to 0.7 mg/m^2 BSA.
g. If no infusion-related side effects occurred, post-medication with corticosteroids was administered from Cycle 7 at the investigator's discretion.
h. Exception: 160 mg dexamethasone (or equivalent) as maximum exposure before randomization.
i. Exception: patients undergoing maintenance treatment with steroids (≤ 20 mg/day or equivalent) due to other diseases.

AE: adverse event; AL amyloidosis: light chain amyloidosis; BMI: body mass index; BSA: body surface area; CD: cluster of differentiation; COPD: chronic obstructive pulmonary disease; CYP3A4: cytochrome P450 3A4; IV: intravenous; RCT: randomized controlled trial; SC: subcutaneous; VCd: bortezomib + cyclophosphamide + dexamethasone

The ANDROMEDA study is an open-label RCT comparing daratumumab + VCd versus VCd and is already known from an earlier benefit assessment procedure [3]. The study included adults with newly diagnosed systemic AL amyloidosis. In addition to a histopathologic diagnosis, a measurable disease had to be present, defined by exceeding defined threshold values of serum M-protein and/or free light chains in the serum (see Table 6). Patients should have at least 1 organ affected by AL amyloidosis and an ECOG PS ≤ 2. Patients with abnormal cardiovascular conditions such as (NYHA) stage IIIb or IV heart failure and a planned ASCT within the first 6 cycles of treatment were excluded from participation in the study.

The study included a total of 388 patients, randomly allocated in a 1:1 ratio to the treatment arms daratumumab + VCd (N = 195) or VCd (N = 193). Randomization was stratified according to cardiac stage (Mayo stage I vs. II vs. IIIa), countries that typically offer stem cell transplantation for patients with AL amyloidosis (list A: yes vs. list B: no) and renal function status (creatinine clearance: < 60 mL/min vs. ≥ 60 mL/min). The following countries were defined as countries that typically offer stem cell transplantation for patients with AL amyloidosis: Australia, Brazil, Canada, Germany, Hungary, Italy, Japan, Netherlands, Poland, Romania, South Korea, Spain, Sweden, Turkey, USA, United Kingdom. The following countries were defined as countries that typically do not offer stem cell transplantation: Belgium, China, Denmark, France, Greece, Israel, Mexico.

The study medication was administered in 28-day cycles in both treatment arms. Patients in the intervention arm received daratumumab + VCd in the first 6 cycles and daratumumab as monotherapy from Cycle 7 to a maximum of 24 cycles. Patients in the comparator arm received a maximum of 6 cycles of VCd. Daratumumab + VCd was administered subcutaneously in compliance with the (SmPC) [15]. Treatment with VCd in the comparator arm was carried out in accordance with the administration of VCd in the intervention arm. Patients were treated until disease progression, start of subsequent therapy, unacceptable toxicity or withdrawal of consent. Subsequent therapies, including therapy with daratumumab, were permitted without restriction.

The study's primary outcome is the CHR. Patient-relevant secondary outcomes are overall survival, outcomes on morbidity as well as health-related quality of life and AEs.

Suitability of the patient population included in the ANDROMEDA study for this research question

In the previous benefit assessment procedure, an individualized treatment was defined as ACT for adults with newly diagnosed systemic AL amyloidosis, taking into account general condition, comorbidities and organ damage. The following therapies, all of which are not approved, were considered suitable comparators: bortezomib + cyclophosphamide + dexamethasone, bortezomib ± dexamethasone, bortezomib + melphalan + dexamethasone, lenalidomide + cyclophosphamide + dexamethasone, lenalidomide + dexamethasone, melphalan + dexamethasone, lenalidomide + melphalan + dexamethasone, high-dose melphalan therapy followed by ASCT (immediately or after completed induction) [16,17]. Based on the ANDROMEDA study, statements on the added benefit of daratumumab + VCd compared to individualized treatment under consideration of the general condition, comorbidities and organ damage, could only be derived for the subpopulation of those patients for whom VCd is the suitable therapy for the individual patient. The G-BA specified a time limit of the validity of its decision exclusively for these patients [16,17]. The research question of this benefit assessment thus only comprises adult patients with newly diagnosed

systemic AL amyloidosis for whom VCd is the suitable therapy for the individual patient (see Table 4). At the time of the current assessment, VCd and daratumumab + VCd are the most suitable therapies for the majority of patients included in the study. However, it is uncertain whether treatment with VCd is the most suitable therapy for all patients in the ANDROMEDA study.

For suitable patients with a low risk profile (good performance status and mild impairment of organ function; according to the literature, these patients make up around 20% of all patients with AL amyloidosis), high-dose melphalan therapy followed by ASCT with or without prior induction therapy is recommended [14,18]. In the ANDROMEDA study, the VCd combination administered in the comparator arm is categorized as induction therapy in this case. This means that VCd is also a sufficiently suitable individualized treatment for the population with a low risk profile if it is followed by ASCT or if ASCT can be dispensed with due to the achievement of a complete remission through induction therapy. However, there is uncertainty regarding the option of an ASCT. The ANDROMEDA study was also conducted in countries that typically do not offer stem cell transplantation for patients with systemic AL amyloidosis (see study description above). In the ANDROMEDA study, a total of 24% of patients in the comparator arm had been included in such countries. It is unclear how many of these patients would have been immediately eligible (or in the later course following induction therapy, see section on subsequent therapies) for high-dose melphalan therapy followed by ASCT as an individualized treatment. Overall, the proportion of patients who would have been eligible for ASCT but did not receive such treatment due to the health care situation is estimated to be low in relation to the total population of the ANDROMEDA study.

There is further uncertainty regarding the proportion of patients with a translocation t (11;14) in the plasma cell clone included in the ANDROMEDA study. A potentially poorer response to therapy with bortezomib has been described for this translocation [19,20].

However, the translocation status was only determined in 95 of 195 (49%) patients in the intervention arm and 107 of 193 (55%) patients in the comparator arm in the ANDROMEDA study. In the comparator arm, 55 patients (51% related to the patients with a genetic status determination) had a corresponding translocation. The extent to which this has an impact on the fundamental suitability of a bortezomib-containing treatment regimen for these patients is unclear.

In summary, there is uncertainty in the patient population included in the ANDROMEDA study, particularly due to the proportion of patients who were unable to receive ASCT because of the health care situation. The certainty of conclusions is therefore reduced for all outcomes. Thus, at most hints, e.g. of an added benefit, can be derived for all outcomes on the basis of the effects shown in the ANDROMEDA study.

Data cut-offs

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

- first data cut-off of 14 February 2020 (planned after the last patient had been treated for 6 months)
- second data cut-off of 17 April 2024 (planned after 200 Major Organ Deterioration-Progression Free Survival [MOD-PFS] events have occurred)
- final data cut-off of 15 November 2024 (5 years after randomization of the last patient)

In addition, a further data cut-off was performed after the first data cut-off as part of the 120-day safety update for the Food and Drug Administration (FDA).

In Module 4 A, the company used the results of the second data cut-off (17 April 2024) for the benefit assessment. For the outcomes overall survival and AEs, it also presents the results for the final data cut-off (15 November 2024). For the outcomes of the categories morbidity and health-related quality of life, the final analyses are therefore not available for all relevant outcomes for the relevant final data cut-off (15 November 2024) of the ANDROMEDA study, as in the module template and in accordance with the specifications for the time limit of the validity of the decision [17]. However, the data presented by the company can nevertheless be used for the benefit assessment of daratumumab. This is justified below:

The number of additional surveys of patient-reported outcomes in the final data cut-off (15 November 2024) compared to the second data cut-off (17 April 2024) and their influence on the results is estimated to be very minor, i.e. no essential gain in information pertaining to the patient-reported outcomes is expected from the final data cut-off (15 November 2024) compared to the previous data cut-off (17 April 2024). Therefore, the data cut-off of 17 April 2024 can be used for the assessment of the patient-reported outcomes.

For the outcome major organ deterioration, the final analysis was carried out at the 2nd data cut-off (17 April 2024). As the outcome was not surveyed any further after this, it was appropriate to use the second data cut-off (17 April 2024).

As the recording of the AE outcomes was linked to the treatment duration, these were no longer recorded after the second data cut-off (17 April 2024). Accordingly, the results of the second data cut-off and the final data cut-off are identical.

In summary, this benefit assessment used the final data cut-off (15 November 2024) for the outcomes in the categories mortality and side effects, and the second data cut-off (17 April 2024) for the outcomes in the categories morbidity and health-related quality of life.

Planned duration of follow-up observation

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

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

Study outcome category outcome	Planned follow-up observation
ANDROMEDA	
Mortality	
Overall survival	Until death or end of study[b, c]
Morbidity	
Major organ deterioration	Until occurrence of the outcome MOD-PFS[b, c]
Symptoms (EORTC QLQ-C30, EORTC QLQ individual items)	Up to 32 weeks after the occurrence of the outcome MOD-PFS[b]
Health status (EQ-5D VAS)	Up to 32 weeks after the occurrence of the outcome MOD-PFS[b]
Health-related quality of life (EORTC QLQ-C30, SF-36)	Up to 32 weeks after the occurrence of the outcome MOD-PFS[b]
Side effects	
All outcomes in the side effects category	Up to 30 days after the last dose of the study medication or until the start of a subsequent treatment

a. Five years after randomization of the last patient.
b. The composite outcome MOD-PFS is reached upon the onset of major organ deterioration (for operationalization see Section I 4.1), haematological disease progression or death, whichever occurs first.
c. Information is only available on the planned follow-up period for the composite outcome MOD-PFS. It is assumed that the planned follow-up period for the component major organ deterioration corresponds to that of the composite outcome.

EORTC: European Organisation for Research and Treatment of Cancer; MOD-PFS: Major Organ Deterioration-Progression Free Survival; QLQ-C30: Quality of Life Questionnaire - Core 30; RCT: randomized controlled trial; SF-36: Short Form-36 Health Survey; VAS: visual analogue scale; VCd: bortezomib + cyclophosphamide + dexamethasone

The observation periods were systematically shortened for all outcomes except overall survival. Side effects were only recorded for the period of treatment with the study medication (plus 30 days or until the start of subsequent therapy). Outcomes on morbidity and health-related quality of life were followed-up beyond treatment, i.e. until and beyond disease progression (up to 32 weeks after the occurrence of the outcome MOD-PFS, for the definition of the outcome see Section I 4.1).

In order to draw a reliable conclusion on the total study period or the time to patient death, however, it would be necessary to survey all outcomes over the total period, as was done for survival.

Characteristics of the study populations

Table 9 shows the patient characteristics of the included study.

Table 9: Characteristics of the study population as well as discontinuation of the study/treatment – RCT, direct comparison: daratumumab + VCd vs. VCd (multipage table)

Study characteristic category	Daratumumab + VCd N[a] = 195	VCd N[a] = 193
ANDROMEDA		
Age [years], mean (SD)	62 (10)	64 (10)
< 65 years, n (%)	108 (55)	97 (50)
≥ 65 years, n (%)	87 (45)	96 (50)
Sex [F/M], %	45/55	39/61
Family origin, n (%)		
Asian	30 (15)	34 (18)
Black or African American	6 (3)	7 (4)
White	151 (77)	143 (74)
Other[b]	1 (1)[c]	4 (2)[c]
Unknown	7 (4)	5 (3)
ECOG PS, n (%)		
0	90 (46)	71 (37)
1	86 (44)	106 (55)
2	19 (10)	16 (8)
Isotype of AL amyloidosis, n (%)[d]		
Lambda	158 (81)	149 (77)
Kappa	37 (19)	44 (23)
Time since initial diagnosis [days], median [min; max]	48 [8; 1611]	43 [5; 1102]
Organ involvement, n (%)		
Heart	140 (72)	137 (71)
Kidney	115 (59)	114 (59)
Liver	15 (8)	16 (8)
Gastrointestinal tract	30 (15)	29 (15)
Lung	3 (2)	5 (3)
Nerves	42 (22)	33 (17)
Soft tissue	51 (26)	55 (29)
Number of organs involved, median [min; max]	2 [1; 5]	2 [1; 6]
1 organ, n (%)	66 (34)	68 (35)
2 organs, n (%)	76 (39)	77 (40)
≥ 3 organs, n (%)	53 (27)	48 (25)

Table 9: Characteristics of the study population as well as discontinuation of the study/treatment – RCT, direct comparison: daratumumab + VCd vs. VCd (multipage table)

Study characteristic category	**Daratumumab + VCd** **N[a] = 195**	**VCd** **N[a] = 193**
Cardiac stage[e], n (%)		
Stage I	47 (24)	43 (22)
Stage II	76 (39)	80 (42)
Stage IIIa	70 (36)	64 (33)
Stage IIIb	2 (1)	6 (3)
Stage of NYHA, n (%)		
Stage I	101 (52)	94 (49)
Stage II	77 (40)	89 (46)
Stage IIIa	17 (9)	10 (5)
Chronic renal insufficiency, n (%)[f]		
Stage I	60 (31)	55 (29)
Stage II	69 (35)	76 (39)
Stage III	51 (26)	41 (21)
Stage IV	14 (7)	21 (11)
Stage V	1 (1)	0
Cytogenetic risk profile, n (%)[g]		
High risk	17 (11[h])	19 (11[h])
Standard risk	138 (89[h])	147 (89[h])
Residence in a country that typically offers stem cell transplantation for patients with AL amyloidosis, n (%)		
Yes	147 (75)	146 (76)
No	48 (25)	47 (24)
Treatment discontinuation, n (%)[i]	69 (36)	68 (35)
Study discontinuation, n (%)[j]	54 (28)	90 (47)

Table 9: Characteristics of the study population as well as discontinuation of the study/treatment – RCT, direct comparison: daratumumab + VCd vs. VCd (multipage table)

Study characteristic category	Daratumumab + VCd N[a] = 195	VCd N[a] = 193

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Summary: native Americans and Alaskans, native Hawaiians or other Pacific Islanders, and multiple family origins.
c. Institute's calculation.
d. Based on immunofixation or measurement of free light chains.
e. Mayo stage based on the combination of the risk factors N-terminal pro-brain natriuretic peptide (NT-proBNP) (threshold value > 332 ng/L) and high-sensitivity cardiac troponin T (hs-cTnT) (threshold value > 54 ng/L). In accordance with the protocol, study participants in stage IIIb were excluded from participation in the study. All study participants had stage IIIa at screening, but some progressed to stage IIIb by Day 1 of Cycle 1.
f. Based on the estimated glomerular filtration rate (eGFR).
g. The assessment of the cytogenetic risk is based on fluorescence in situ hybridization (FISH) or karyotyping related to the following high-risk markers: del(17p), t(4;14) and t(14;16). High-risk defined as: t (4; 14), t (14; 16), del17p (by FISH testing) or t (4; 14), del17p (by karyotyping).
h. Related to 155 (intervention arm) and 166 (comparator arm) patients with available assessment of the cytogenetic risk.
i. Treatment discontinuation before reaching the maximum number of cycles planned according to the protocol. The information refers to the second data cut-off (17 April 2024). Common reasons for treatment discontinuation in the intervention versus the control arm were (percentages refer to randomized patients): death (12% vs. 7%), receipt of subsequent therapy (3% vs. 12%), AEs (6% vs. 4%), disease progression (MOD-PFS) (4% vs. 6%), withdrawal of consent (3% vs. 4%), receipt of ASCT (6% vs. 2%). This includes 2 vs. 5 patients who never started therapy.
j. The information refers to the second data cut-off (17 April 2024). The reasons for study discontinuation were: death (24% vs. 33%), withdrawal of consent (4% vs. 12%) and lost to follow-up (0% vs. 2%).

ASCT: autologous stem cell transplantation; ECOG PS: Eastern Cooperative Oncology Group - Performance Status; f: female; FISH: fluorescence in situ hybridisation; hs-cTNT: high-sensitivity cardiac troponin T; m: male; MOD-PFS: Major Organ Deterioration-Progression-Free Survival; n: number of patients in the category; N: number of randomized patients; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; RCT: randomized controlled trial; SD: standard deviation; VCd: bortezomib + cyclophosphamide + dexamethasone

Patient characteristics between the 2 treatment groups of the ANDROMEDA study are sufficiently balanced. The mean age of the patients was 62 and 64 years, and the majority (76%) were white. The proportion of women in the daratumumab + VCd arm was slightly higher (45%) than in the comparator arm (39%). 9% of the patients included had an ECOG PS of 2. 26% of the patients had ≥ 3 organs affected by amyloidosis. The most frequently affected organs were the heart (71%) and the kidneys (59%). Overall, 24% of the patients included in the study resided in a country that does not typically offer stem cell transplantation for patients with AL amyloidosis.

Study discontinuation was less frequent in the daratumumab + VCd arm than in the comparator arm (28% vs. 47%).

Course of the study

Table 10 shows patients' mean and median treatment durations as well as the median observation period for individual outcomes or outcome categories.

Table 10: Information on the course of the study – RCT, direct comparison: daratumumab + VCd vs. VCd (multipage table)

Study **duration of the study phase** **data cut-off** **outcome category/outcome**	**Daratumumab + VCd** **N = 195**	**VCd** **N = 193**
ANDROMEDA		
Treatment duration [months]		
Data cut-off 17 April 2024		
Median [min; max][a]	21.3 [0.0; 26.7]	5.3 [0.0; 7.3]
Mean (SD)	16.6 (8.5)	4.4 (1.7)
Data cut-off 15 November 2024		
Median [min; max][a]	21.3 [ND]	5.3 [ND]
Mean (SD)	ND	ND
Observation period [months]		
Data cut-off 15 November 2024		
Overall survival		
Median[b] [min; max]	68.8 [ND]	67.7 [ND]
Mean (SD)	ND	ND
Data cut-off 17 April 2024		
Morbidity (major organ deterioration[c])		
Median[b] [min; max]	60.6 [ND]	58.9 [ND]
Mean (SD)	ND	ND
Morbidity, health-related quality of life (EORTC QLQ-C30; EORTC QLQ individual items[d]; EQ-5D VAS, SF-36)		
Median[e] [min; max]	34.5 [ND]	6.2 [ND]
Mean (SD)	ND	ND
Data cut-off 15 November 2024		
Side effects		
Median[f] [min; max]	22.2 [ND]	6.3 [ND]
Mean (SD)	ND	ND

Table 10: Information on the course of the study – RCT, direct comparison: daratumumab + VCd vs. VCd (multipage table)

Study **duration of the study phase** **data cut-off** **outcome category/outcome**	**Daratumumab + VCd** **N = 195**	**VCd** **N = 193**
a. The maximum treatment duration was 24 cycles (28 days each) in the intervention arm and 6 cycles (28 days each) in the comparator arm. 3 patients in the intervention arm were treated for 25 cycles. b. Inverse Kaplan-Meier method. c. Data for the composite outcome MOD-PFS. d. From the disease-specific modules EORTC QLQ-MY20, EORTC QLQ-OV28, EORTC QLQ-PR25. e. Based on the last survey date before the subsequent therapy. It is unclear why the company did not consider planned surveys after the start of a subsequent therapy when calculating the observation periods. f. Data based on the time of the individualized treatment duration +30 days. EORTC: European Organisation for Research and Treatment of Cancer max: maximum; min: minimum; MOD-PFS: Major Organ Deterioration-Progression-Free Survival; N: number of analysed patients; ND: no data; QLQ-C30: Quality of Life Questionnaire - Core 30; QLQ-MY20: Quality of Life Questionnaire - Multiple Myeloma 20; QLQ-OV28: Quality of Life Questionnaire - Ovarian Cancer 28; QLQ-PR25: Quality of Life Questionnaire - Prostate Cancer 25; RCT: randomized controlled trial; SD: standard deviation; SF-36: Short Form-36 Health Survey; VAS: visual analogue scale; VCd: bortezomib + cyclophosphamide + dexamethasone		

The median and mean treatment duration for the second data cut-off (17 April 2024) and the final data cut-off (15 November 2024) are identical since at the time of the second data cut-off (17 April 2024) no patient was still being treated with the study medication due to the limitation of treatment durations in the intervention and comparator arm. The median treatment duration in the intervention arm was longer than in the comparator arm (21.3 months vs. 5.3 months) due to the longer planned treatment duration of a maximum of 24 cycles in the intervention arm compared to a maximum of 6 cycles in the comparator arm.

At the time of the final analysis on overall survival, the median observation period for the outcome overall survival was similar between the two treatment arms (68.8 months in the intervention arm and 67.7 months in the comparator arm).For the outcome severe organ damage, the median observation period differed only slightly between the treatment groups. As the observation period for the outcomes on side effects is linked to the treatment duration (see Table 8), the observation period in the intervention arm is also longer here than in the comparator arm (22.2 vs. 6.3 months). The patient-reported outcomes morbidity and health-related quality of life were recorded at different frequencies in the study arms, among other things depending on the treatment duration (see Section I 4.2) and have a longer observation period in the intervention arm (34.5 months) than in the comparator arm (6.2 months).

The information provided by the company on the median duration of observation for the patient-reported outcomes is based on the time up to the last survey before the start of subsequent therapy ("prior to subtherapy"). It is unclear why the company did not consider

planned surveys after the start of a subsequent therapy when calculating the observation periods.

Subsequent therapies

In Module 4 A, the company provides information on subsequent therapies aggregated across all treatment lines at both the drug and treatment regimen level. In addition, information is also available on subsequent therapies in the form of treatment regimens in the individual treatment lines. The information refers exclusively to the second data cut-off (17 April 2024). There is no information available at the final cut-off (15 November 2024). It is assumed that this has no effect on the results of the outcome overall survival. Since only 1 additional death occurred in each arm between the second data cut-off (17 April 2024) and the final data cut-off (15 November 2024), no essential gain in information compared to the second data cut-off is to be expected through potential further subsequent therapies. The information on subsequent therapies at the second data cut-off is therefore considered in the present situation.

Patients in the intervention arm received at most 4 subsequent therapies, those in the comparator arm received at most 6. This benefit assessment considers the data on the first subsequent therapy; see the following Table 11.

Table 11: Information on the first subsequent therapy – RCT, direct comparison: daratumumab + VCd vs. VCd (multipage table)

Study **drug/drug combination**	**Patients with subsequent therapy, n (%)**	
	daratumumab + VCd **N = 193**	**VCd** **N = 188**
ANDROMEDA (data cut-off: 17 April 2024)		
Total	61 (31.6)	122 (64.9)
ASCT	ND[a]	ND[a]
Melphalan	16 (26.2[b])	14 (11.5[b])
Daratumumab	8 (13.1[b])	19 (15.6[b])
Dexamethasone-lenalidomide	6 (9.8[b])	9 (7.4[b])
Daratumumab-dexamethasone-lenalidomide	5 (8.2[b])	14 (11.5[b])
Dexamethasone-melphalan	3 (4.9[b])	5 (4.1[b])
Bortezomib-cyclophosphamide-daratumumab-dexamethasone	2 (3.3[b])	1 (0.8[b])
Daratumumab-dexamethasone	2 (3.3[b])	3 (2.5[b])
Dexamethasone-pomalidomide	2 (3.3[b])	3 (2.5[b])
Dexamethasone-venetoclax	2 (3.3[b])	0 (0[b])
Monoclonal antibodies	2 (3.3[b])	0 (0[b])
Venetoclax	2 (3.3[b])	0 (0[b])

Table 11: Information on the first subsequent therapy – RCT, direct comparison: daratumumab + VCd vs. VCd (multipage table)

Study drug/drug combination	Patients with subsequent therapy, n (%)	
	daratumumab + VCd N = 193	VCd N = 188
Bortezomib	1 (1.6[b])	1 (0.8[b])
Bortezomib-daratumumab-dexamethasone-lenalidomide	1 (1.6[b])	0 (0[b])
Bortezomib-dexamethasone-venetoclax	1 (1.6[b])	0 (0[b])
Carfilzomib-dexamethasone-lenalidomide	1 (1.6[b])	0 (0[b])
Cyclophosphamide-melphalan	1 (1.6[b])	1 (0.8[b])
Daratumumab-pomalidomide	1 (1.6[b])	1 (0.8[b])
Dexamethasone-isatuximab-pomalidomide	1 (1.6[b])	1 (0.8[b])
Dexamethasone-ixazomib citrate-lenalidomide	1 (1.6[b])	0 (0[b])
Dexamethasone-ixazomib-lenalidomide	1 (1.6[b])	0 (0[b])
Investigational drug	1 (1.6[b])	0 (0[b])
Melphalan-prednisone	1 (1.6[b])	0 (0[b])
Bendamustine-dexamethasone	0 (0[b])	1 (0.8[b])
Bortezomib-cyclophosphamide monohydrate-dexamethasone	0 (0[b])	2 (1.6[b])
Bortezomib-cyclophosphamide-dexamethasone	0 (0[b])	11 (9.0[b])
Bortezomib-cyclophosphamide-dexamethasone-investigational drug	0 (0[b])	1 (0.8[b])
Bortezomib-daratumumab	0 (0[b])	1 (0.8[b])
Bortezomib-daratumumab-dexamethasone	0 (0[b])	10 (8.2[b])
Bortezomib-daratumumab-dexamethasone-pomalidomide-dexamethasone-pomalidomide-daratumumab	0 (0[b])	1 (0.8[b])
Bortezomib-dexamethasone-lenalidomide	0 (0[b])	3 (2.5[b])
Bortezomib-dexamethasone-melphalan	0 (0[b])	1 (0.8[b])
Carfilzomib	0 (0[b])	1 (0.8[b])
Clarithromycin-dexamethasone-lenalidomide	0 (0[b])	1 (0.8[b])
Cyclophosphamide-dexamethasone	0 (0[b])	1 (0.8[b])
Cyclophosphamide-dexamethasone-lenalidomide	0 (0[b])	1 (0.8[b])
Daratumumab-dexamethasone-lenalidomide-prednisone	0 (0[b])	1 (0.8[b])
Daratumumab-dexamethasone-pomalidomide	0 (0[b])	2 (1.6[b])
Daratumumab-lenalidomide	0 (0[b])	2 (1.6[b])
Daratumumab-melphalan	0 (0[b])	1 (0.8[b])
Daratumumab-prednisone	0 (0[b])	1 (0.8[b])
Dexamethasone- investigational antineoplastic drug - pomalidomide	0 (0[b])	1 (0.8[b])
Dexamethasone-lenalidomide-melphalan	0 (0[b])	1 (0.8[b])
Isatuximab	0 (0[b])	1 (0.8[b])

Table 11: Information on the first subsequent therapy – RCT, direct comparison: daratumumab + VCd vs. VCd (multipage table)

Study drug/drug combination	Patients with subsequent therapy, n (%)	
	daratumumab + VCd N = 193	VCd N = 188
Lenalidomide	0 (0[b])	1 (0.8[b])
Melphalan hydrochloride	0 (0[b])	2 (1.6[b])
Melphalan-other blood product	0 (0[b])	1 (0.8[b])
Other antineoplastic drugs	0 (0[b])	1 (0.8[b])

a. There is no information on ASCT in the first subsequent therapy, only information on ASCT in any subsequent therapies; the information on this is discrepant within Module 4 A, the information presented here corresponds to the information from the study report: According to the information in the study report, 17 patients in the intervention arm vs. 27 patients in the comparator arm received ASCT as subsequent therapy. It is unclear how many patients received ASCT as part of a first-line treatment (see running text).
b. Percentages: Institute's calculation, based on the number of patients with subsequent therapy.

ASCT: autologous stem cell transplantation; n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial; VCd: bortezomib + cyclophosphamide + dexamethasone

According to the study protocol, patients should not receive any subsequent therapy before the first 6 cycles have been completed, unless the MOD-PFS outcome had been reached. Nevertheless, treatment could be discontinued from Cycle 4 onwards if there was a haematological response and a deterioration in organ function.

From Cycle 7 onwards, the study protocol provided precise recommendations for the subsequent therapy. Depending on the haematological response and organ function, either i) continuation of daratumumab as monotherapy (in the intervention arm) or further observation (in the comparator arm) until progression, ii) subsequent therapy could be considered or iii) subsequent therapy could be recommended. Further observation in the control arm was only recommended without restriction if there had been a response (i.e. partial response [PR] or better) in the first 6 cycles and organ function had also improved since the start of treatment. In other cases, subsequent therapy should be considered; in the absence of a haematological response and simultaneous deterioration in organ function, it was explicitly recommended in the study protocol. These guidelines largely correspond to the treatment recommendations [18-21].

There were no restrictions regarding subsequent therapies in the ANDROMEDA study.

61 (31.6%) patients in the intervention arm and 122 (64.9%) patients in the comparator arm of the ANDROMEDA study had received at least one subsequent therapy by the second data cut-off (17 April 2024). In relation to patients with subsequent therapy, the most frequently

used drugs or drug combinations in the first subsequent therapy were melphalan (26%) in the intervention arm and daratumumab (15.6%), melphalan (11.5%) and daratumumab in combination with dexamethasone and lenalidomide (11.5%) in the comparator arm. 17 (8.8%) patients in the intervention arm and 27 (14.4%) patients in the comparator arm received ASCT in one of the following lines of treatment. It is unclear whether the company's information on melphalan therapy as the first subsequent therapy includes high-dose melphalan therapies administered prior to ASCT. Information on the implementation of ASCT (including prior high-dose melphalan therapy) as first subsequent therapy is not available. The study documents only state that ASCT was the reason for starting the first subsequent therapy in 9 patients in the intervention arm and 11 patients in the comparator arm. There is uncertainty as to whether these patients received ASCT as a subsequent therapy or as part of the first-line treatment strategy. High-dose melphalan therapy followed by ASCT with or without prior induction therapy is recommended for suitable patients with a low risk profile [14,18]. The study medication can be considered a suitable induction therapy in both the intervention and the comparator arm. Accordingly, high-dose therapy with melphalan followed by ASCT after administration of the study medication could be part of the first-line treatment for some of the patients. With regard to the 17 or 27 patients who received ASCT in one of the subsequent treatment lines according to the information in Module 4 A, it is unclear how many of the patients received ASCT as part of first-line treatment. It should also be noted that, according to the study protocol, patients with a planned ASCT within the first 6 cycles of treatment with the study medication were excluded from participation in the study.

From the second line onwards, no drugs are allowed in this therapeutic indication. For patients with systemic AL amyloidosis with progression, recurrence or refractory disease, guidelines list a wide range of treatment options, including monotherapies, dual or triple combination therapies [14,18,20,21]. However, the treatment recommendations are mainly based on data with a low level of evidence, such as retrospective analyses and smaller phase II studies. The therapy should be chosen depending on the individual pretreatment, patient preference and toxicity profile. Repetition of first-line therapy can be considered for patients who have been recurrence-free for several years [14,18]. Daratumumab-containing therapy is particularly recommended for patients who have not yet been treated with daratumumab [14,18,20,22].. In the comparator arm of the ANDROMEDA study, patients are treatment-naive regarding the treatment with daratumumab. A total of 57 patients in the comparator arm (47% based on patients with subsequent therapy) received daratumumab-based therapy as their first subsequent therapy. Daratumumab-based treatment in any line of therapy was administered to 82 patients in the comparator arm (67.2% of patients with subsequent therapy).

In summary, there is little evidence of treatment recommendations for patients with newly diagnosed AL amyloidosis in the second line. The therapies used in the first subsequent therapy of the ANDROMEDA study as well as the daratumumab-based treatments

administered in any therapy line largely correspond to the therapy recommendations in the guidelines.

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 + VCd versus VCd

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

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

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

Transferability of the study results to the German health care context

The company described that the ANDROMEDA study was conducted in 22 countries due to the rareness of the disease. According to the company, there are no indications of relevant effect differences with regard to the family origin. Furthermore, the stratification characteristic "countries that typically offer stem cell transplantation for patients with AL amyloidosis (list A: yes/list B: no)" also showed no indications of effect differences. Finally, the company describes that there were no indications of biodynamic or kinetic differences between the population groups or countries involved and Germany to the extent that they would have a pronounced impact on the study results. Therefore, the company deems it safe to assume that, when taking into account the uncertainty associated with the transferability of clinical data, the results are in principle transferable to the German health care context.

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

I 4 Results on added benefit

I 4.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - major organ deterioration
  - symptoms recorded with the EORTC QLQ-C30
  - symptoms, assessed with the individual items of the EORTC QLQ from the disease-specific modules EORTC QLQ-Ovarian Cancer 28 (OV28), Multiple Myeloma 20 (MY20) and Prostate Cancer 25 (PR25)
  - health status, recorded using the EQ-5D VAS
- Health-related quality of life
  - recorded with the EORTC QLQ-C30
  - recorded using the SF-36
- Side effects
  - SAEs
  - severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to AEs
  - peripheral neuropathies (high level term [HLT], AEs)
  - other specific AEs, if any

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

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

Table 13: Matrix of outcomes – RCT, direct comparison: daratumumab + VCd versus VCd

Study	Outcomes									
	Overall survival	Major organ deterioration[a]	Symptoms (EORTC QLQ-C30, EORTC QLQ individual items[b])	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30, SF-36)	SAEs	Severe AEs[c]	Discontinuation due to AEs[d]	Peripheral neuropathies (HLT, AEs[e])	Other specific AEs[f]
ANDROMEDA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Defined as occurrence of one of the following events:
- clinical manifestation of heart failure, defined as the need for a heart transplant, a left ventricular assist device or an intra-aortic balloon pump.
- clinical manifestation of renal failure, defined as the development of end-stage renal disease (need for haemodialysis or kidney transplantation).

b. The individual items tingling in the hands and feet from the EORTC QLQ-MY20, feeling of fullness in the abdomen/stomach from the EORTC QLQ-OV28 and swelling of the legs or ankles from the EORTC QLQ-PR25 are considered.
c. Operationalized as CTCAE grade ≥ 3.
d. Discontinuation of ≥ 1 drug component.
e. Operationalized as symptomatic peripheral neuropathies (CTCAE grade ≥ 2).
f. The following events were considered (MedDRA coding): skin and subcutaneous tissue disorders (SOC, AEs), hypokalaemia (PT, severe AEs) [operationalized as CTCAE grade ≥ 3].

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HLT: High Level Term; MedDRA: Medical Dictionary for Drug Regulatory Activities; PT: Preferred Term; QLQ-MY20: Quality of Life Questionnaire - Multiple Myeloma 20; QLQ-OV28: Quality of Life Questionnaire - Ovarian Cancer 28; QLQ-PR25: Quality of Life Questionnaire - Prostate Cancer 25; QLQ-C30: Quality of Life Questionnaire - Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form-36 Health Survey; SOC: System Organ Class; VAS: visual analogue scale; VCd: bortezomib + cyclophosphamide + dexamethasone

Major organ deterioration

In its dossier, the company presents results for the composite outcome severe organ damage for the second data cut-off (17 April 2024). The outcome was operationalized as time to occurrence of any of the following events:

- clinical manifestation of heart failure, defined as the need for a heart transplant, a left ventricular assist device or an intra-aortic balloon pump
- clinical manifestation of renal failure, defined as the development of end-stage renal disease (need for haemodialysis or kidney transplantation)

The outcome is a component of the composite outcome MOD-PFS, operationalized over the time to the occurrence of major organ deterioration, haematological disease progression or death. Haematological disease progression is present if ≥ 1 of the following criteria is met:

- starting from a complete haematological response (CHR): abnormal free light chain ratio (doubling of the light chains)
- based on CHR, very good partial response (VGPR) or partial response (PR): increase in serum M protein by 50% to an absolute value of serum M protein > 0.5 g/dL or increase in urine M protein by 50% to an absolute value of urine M protein > 200 mg/day
- increase in the free light chains involved by > 50% to > 100 mg/L

In this benefit assessment, the components major organ deterioration and death (overall survival) are considered as independent patient-relevant outcomes. The composite outcome MOD-PFS itself is not included in the benefit assessment, as the component haematological disease progression is an outcome based purely on laboratory parameters.

EORTC QLQ-C30

In its dossier, the company presented responder analyses for patient-reported outcomes on morbidity and health-related quality of life, recorded with the EORTC QLQ-C30, for the time to the first change by ≥ 10 points (scale range 0 to 100). These are used for the benefit assessment.

Individual items of the EORTC QLQ-OV28, -MY20 and -PR25

In its dossier, the company presented results on the individual items prespecified in the study protocol, i.e. tingling in the hands and feet from the EORTC QLQ-MY20, feeling of fullness in the abdomen/stomach from the EORTC QLQ-OV28 and swelling of the legs or ankles from the EORTC QLQ-PR25. In the study protocol, the use of these items is justified with the Lin 2015 publication on the symptoms of AL amyloidosis [23]. The individual items were not used for the benefit assessment in the initial assessment in 2021 (dossier assessment A21-100 [3]), as the selection of the 3 items by the company was not comprehensibly justified and, at the time of the assessment at that time, the EORTC only intended the use of individual items as an item list in conjunction with the EORTC QLQ-C30 and an already validated disease-specific additional module [24]. According to the current version of the User Guidelines for the EORTC Item Library, the use of individual items is no longer tied to the presence of an additional module [25].

In the 2015 publication by Lin, 25 symptoms were initially identified with the involvement of patients with AL amyloidosis, of which the company used the 11 most frequently mentioned as core symptoms. In Module 4 A of this dossier, the company comprehensibly describes that 7 of these symptoms are already covered by the core questionnaire EORTC QLQ-C30. This does

not apply to the symptoms of numbness/tingling, oedema in the upper abdomen (feeling of fullness, bloated abdomen, swollen arms or legs), oedema in the lower abdomen (swelling of the ankles and feet) and dizziness. The company selected the above-mentioned items tingling in the hands and feet (EORTC QLQ-MY20), feeling of fullness in the stomach/abdomen (EORTC QLQ-OV28) and swelling of the legs or ankles (EORTC QLQ-PR25) from the EORTC item library for the recording of the first 3 symptoms mentioned in the planning of the ANDROMEDA study. Another symptom mentioned in Lin 2015 (dizziness) was not used by the company because, according to its statement in Module 4 A, it was a non-specific symptom that could not be attributed to amyloidosis. In view of the fact that, in contrast to the dossier of the initial assessment [26], the company comprehensibly justified the selection of the items in the dossier and the use of individual items is no longer necessarily linked to the presence of an additional module, they are used in the present assessment in deviation from the procedure in the initial assessment A21-100.

General comment on submitted responder analyses for the patient-reported outcomes

For the outcomes of symptoms and health-related quality of life, which were recorded with the EORTC QLQ-C30, the EORTC QLQ individual items, the SF-36 and the EQ-5D VAS, the company presented responder analyses over the time to first deterioration and over the time to first improvement. The time to first deterioration was used. Given the course of disease to be expected in this therapeutic indication and taking into account the distribution of absolute scale values at baseline, an analysis of a deterioration of the health status is of primary relevance in this benefit assessment.

Side effects

According to the study protocol, progression events of the systemic AL amyloidosis were not recorded as AEs. Information on the definition of non-recorded progression events is not available.

Discontinuation due to AEs

In Module 4 A, the company presents analyses on both the discontinuation of all drug components and ≥ 1 drug component for the outcome discontinuation due to AEs. Analyses on the discontinuation of ≥ 1 drug component were used, as any AE leading to discontinuation of any drug component is relevant.

Peripheral neuropathies (HLT, AEs)

In Module 4 A, the company presents analyses on peripheral neuropathies without severity as well as those with a CTCAE grade ≥ 2 for the outcome peripheral neuropathies. Patient-relevant, symptomatic peripheral neuropathies, i.e. neuropathies with a CTCAE grade ≥ 2, are of interest.

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 + VCd versus VCd

Study	Outcomes										
	Study level	Overall survival	Major organ deterioration[a]	Symptoms (EORTC QLQ-C30, EORTC QLQ individual items[b])	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30, SF-36)	SAEs	Severe AEs[c]	Discontinuation due to AEs[d]	Peripheral neuropathies (HLT, AEs)[e]	Other specific AEs[f]
ANDROMEDA	L	L	H[g]	H[h, i]	H[h, i]	H[h, i]	H[g]	H[g]	H[g, j]	H[g, h]	H[g, k]

a. Defined as occurrence of one of the following events:
- clinical manifestation of heart failure, defined as the need for a heart transplant, a left ventricular assist device or an intra-aortic balloon pump.
- Clinical manifestation of renal failure, defined as the development of end-stage renal disease (need for haemodialysis or kidney transplantation).

b. The individual items tingling in the hands and feet from the EORTC QLQ-MY20, feeling of fullness in the abdomen/stomach from the EORTC QLQ-OV28 and swelling of the legs or ankles from the EORTC QLQ-PR25 are considered.
c. Operationalized as CTCAE grade ≥ 3.
d. Discontinuation of ≥ 1 drug component.
e. Operationalized as symptomatic peripheral neuropathies (CTCAE grade ≥ 2).
f. The following events were considered (MedDRA coding): skin and subcutaneous tissue disorders (SOC, AEs), hypokalaemia (PT, severe AEs) [operationalized as CTCAE grade ≥ 3].
g. Incomplete observations for potentially informative reasons.
h. Lack of blinding in subjective recording of outcomes.
i. Difference in the recording intervals between the treatment arms.
j. Lack of blinding in subjective decision for discontinuation.
k. Only for skin and subcutaneous tissue disorders (SOC, 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; HLT: High Level Term; MedDRA: Medical Dictionary for Drug Regulatory Activities; PT: Preferred Term; QLQ-MY20: Quality of Life Questionnaire - Multiple Myeloma 20; QLQ-OV28: Quality of Life Questionnaire - Ovarian Cancer 28; QLQ-PR25: Quality of Life Questionnaire - Prostate Cancer 25; QLQ-C30: Quality of Life Questionnaire - Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form-36 Health Survey; SOC: System Organ Class; VAS: visual analogue scale; VCd: bortezomib + cyclophosphamide + dexamethasone

With the exception of the outcome overall survival, the risk of bias for the results on all other outcomes was rated as high. The respective reasons for a high risk of bias are described below.

The risk of bias for the outcome major organ deterioration was rated as high. The outcome is a component of the composite outcome MOD-PFS, defined as the occurrence of major organ deterioration, haematological disease progression or death. For the outcome MOD-PFS, a follow-up is planned up to the occurrence of the first event of one of the 3 components. This means that the follow-up of the component major organ deterioration ends prematurely if haematological disease progression has previously occurred. As a result, the observations are incomplete for potentially informative reasons.

In each case, the risk of bias of the results on health status (EQ-5D VAS) and the outcomes of symptoms (EORTC QLQ-C30 symptom scales and EORTC QLQ individual items) and health-related quality of life (EORTC QLQ-C30 functional scales and the scale of global health status, SF-36) is rated as high in each case. This is due to lack of blinding in subjective recording of outcomes. Another aspect is the difference in the recording intervals of the patient-reported outcomes between the treatment arms during the course of the study. The rationale is provided below.

Recordings on the patient-reported outcomes were planned as follows:

- Cycles 1–6: on Day 1 each
- From Cycle 7: every 8 weeks (only in the daratumumab + VCd arm), always on day 1
- 30 days after the end of treatment
- At the start of a subsequent therapy
- every 6 months until the outcome MOD-PFS is reached (at most until a total of 200 MOD-PFS events are reached)
- 16 weeks and 32 weeks after the outcome MOD-PFS is reached

The planned treatment duration was 24 cycles in the intervention arm and 6 cycles in the comparator arm. In the first 6 cycles, the recordings took place on Day 1 of each cycle in both study arms if the medication was not discontinued prematurely. Due to the planned different treatment durations, the study protocol stipulated intervals between the recordings that are longer in the comparator arm than in the intervention arm from Cycle 8 onwards at the latest: from Cycle 7 onwards, recordings were conducted every 8 weeks in the intervention arm, whereas in the comparator arm they were initially conducted 30 days after the last medication (corresponds to the start of Cycle 7 if the medication was not discontinued prematurely) and then only every 6 months until disease progression. As a result, a deterioration, which is used

as operationalization in this benefit assessment, may be detected much later in the comparator arm (or even overlooked) than in the intervention arm.

The risk of bias was rated as high for the results of each of the outcomes of the side effects category. All events that occurred up to 30 days after the last administration of the study medication or up to the start of a subsequent anti-plasma cell therapy were included in the analyses of the outcomes in the side effects category. Due to the difference in the planned treatment duration (24 cycles versus 6 cycles), events occurring up to approximately 2 years after the start of treatment in the intervention arm are taken into account at a cycle duration of 28 days, whereas in the comparator arm only events occurring up to approximately 7 months after the start of treatment are taken into account. As the follow-up is linked to the treatment duration, the observations are incomplete for potentially informative reasons. In addition, the risk of bias for the outcomes discontinuation due to AEs and the specific AEs skin and subcutaneous tissue disorders (AEs) and peripheral neuropathy (AEs) is rated as high due to lack of blinding in subjective recording of outcomes.

I 4.3 Results

Table 15 summarizes the results on the comparison of daratumumab + VCd versus VCd in patients with newly diagnosed systemic AL amyloidosis. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

The Kaplan-Meier curves for the time-to-event analyses of the outcomes in the ANDROMEDA study are shown in I Appendix B of the full dossier assessment. Only the Kaplan-Meier curves on the second data cut-off (17 April 2024) are available for the AE outcomes. However, as no further recordings are added at the final data cut-off, the Kaplan-Meier curves are shown for the second data cut-off (17 April 2024). The results on common AEs, SAEs, severe AEs and discontinuations due to AEs can be found in I Appendix C of the full dossier assessment.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: daratumumab + VCd versus VCd (multipage table)

Study outcome category outcome	Daratumumab + VCd		VCd		Daratumumab + VCd vs. VCd
	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[b]
ANDROMEDA					
Mortality (data cut-off 15 November 2024)					
Overall survival	195	NA 47 (24.1)	193	NA 67 (34.7)	0.62 [0.42; 0.90]; 0.011

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: daratumumab + VCd versus VCd (multipage table)

Study outcome category outcome	Daratumumab + VCd N	Daratumumab + VCd median time to event in months [95% CI] patients with event n (%)	VCd N	VCd median time to event in months [95% CI] patients with event n (%)	Daratumumab + VCd vs. VCd HR [95% CI][a]; p-value[b]
Morbidity (data cut-off: 17 April 2024)					
Major organ deterioration[c]	195	NA 3 (1.5)	193	NA 11 (5.7)	0.22 [0.06; 0.79]; 0.011
Clinical manifestation of heart failure, defined as the need for a heart transplant, a left ventricular assist device or an intra-aortic balloon pump	195	NA 1 (0.5)[d]	193	NA 1 (0.5)[d]	–
Clinical manifestation of renal failure, defined as the development of end-stage renal disease (need for haemodialysis or kidney transplantation)	195	NA 2[e] (1.0)$_d$	193	NA 10 (5.2)[d]	–
Symptoms (EORTC QLQ-C30 – time to first deterioration[f, g])					
Fatigue	195	2.14 [1.94; 3.71] 122 (62.6)	193	1.94 [1.87; 2.83] 128 (66.3)	0.81 [0.63; 1.04]; 0.100
Nausea and vomiting	195	29.21 [9.43; NC] 82 (42.1)	193	40.80 [4.83; NC] 78 (40.4)	0.87 [0.64; 1.19]; 0.390
Pain	195	3.98 [2.86; 7.42] 130 (66.7)	193	3.81 [2.86; 5.16] 106 (54.9)	1.09 [0.84; 1.42]; 0.516
Dyspnoea	195	29.04 [12.98; NC] 84 (43.1)	193	3.81 [2.79; 6.37] 95 (49.2)	0.71 [0.53; 0.97]; 0.029
Insomnia	195	4.67 [3.02; 18.69] 107 (54.9)	193	4.60 [2.89; 15.80] 99 (51.3)	1.00 [0.76; 1.33]; 0.984
Appetite loss	195	9.27 [4.47; 22.64] 99 (50.8)	193	5.78 [3.75; 15.84] 93 (48.2)	0.92 [0.69; 1.23]; 0.580
Constipation	195	NA 56 (28.7)	193	NA 51 (26.4)	1.01 [0.75; 1.34]; 0.969
Diarrhoea	195	7.85 [4.67; 49.74] 99 (50.8)	193	6.44 [3.81; 14.65] 93 (48.2)	0.92 [0.68; 1.23]; 0.565
Symptoms (EORTC QLQ individual items[h]– time to first deterioration[f, g])					
Tingling in hands and feet	195	13.08 [8.77; 60.06] 87 (44.6)	193	11.07 [4.73; 29.93] 88 (45.6)	0.83 [0.62; 1.13]; 0.236
Feeling of fullness in the abdomen/stomach	195	3.88 [2.23; 9.27] 114 (58.5)	193	2.86 [1.94; 3.75] 113 (58.5)	0.89 [0.68; 1.16]; 0.382

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: daratumumab + VCd versus VCd (multipage table)

Study outcome category outcome	Daratumumab + VCd N	Daratumumab + VCd median time to event in months [95% CI] patients with event n (%)	VCd N	VCd median time to event in months [95% CI] patients with event n (%)	Daratumumab + VCd vs. VCd HR [95% CI][a]; p-value[b]
Swelling of the legs or ankles	195	7.20 [3.06; 34.14]; 96 (49.2)	193	4.63 [2.89; 28.58] 92 (47.7)	0.99 [0.74; 1.32]; 0.932
Health status (EQ-5D VAS - time to first deterioration[g, i])	195	17.61 [4.96; 59.17] 90 (46.2)	193	6.24 [3.75; NC] 86 (44.6)	0.93 [0.68; 1.26]; 0.627
Health-related quality of life (data cut-off: 17 April 2024)					
EORTC QLQ-C30 (time to first deterioration[g, j])					
Global health status	195	4.70 [2.96; 7.42] 107 (54.9)	193	2.89 [2.37; 3.78] 114 (59.1)	0.82 [0.63; 1.08]; 0.158
Physical functioning	195	4.73 [2.83; 17.02] 112 (57.4)	193	3.75 [2.83; 4.76] 109 (56.5)	0.86 [0.66; 1.13]; 0.279
Role functioning[k]	195	2.69 [1.94; 4.60] 122 (62.6)	193	2.83 [1.97; 3.68] 122 (63.2)	0.88 [0.68; 1.13]; 0.315
Emotional functioning	195	47.70 [16.69; NC] 76 (39.0)	193	12.22 [4.21; 58.58] 82 (42.5)	0.78 [0.57; 1.08]; 0.135
Cognitive functioning	195	5.58 [4.14; 9.23] 114 (58.5)	193	3.81 [2.83; 4.76] 111 (57.5)	0.85 [0.65; 1.11]; 0.222
Social functioning	195	2.79 [1.94; 3.09] 125 (64.1)	193	2.86 [1.97; 3.75] 114 (59.1)	1.09 [0.84; 1.41]; 0.521
SF-36 (time to first deterioration[g, l])					
Physical Component Summary (PCS)	195	64.39 [32.23; NC] 74 (37.9)	193	24.21 [4.73; 59.70] 79 (40.9)	0.77 [0.55; 1.06]; 0.106
Mental Component Summary (MCS)	195	14.92 [8.12; 54.87] 88 (45.1)	193	28.62 [6.21; NC] 78 (40.4)	1.04 [0.77; 1.42]; 0.788
Side effects (data cut-off: 15 November 2024)					
AEs (supplementary information)	193	0.10 [0.07; 0.13] 190 (98.4)	188	0.18 [0.10; 0.26] 185 (98.4)	–
SAEs	193	NA [9.43; NC] 91 (47.2)	188	NA 68 (36.2)	1.01 [0.73; 1.41]; 0.934
Severe AEs[m]	193	3.61 [2.40; 4.86] 126 (65.3)	188	3.48 [2.53; 4.40] 114 (60.6)	1.01 [0.78; 1.32]; 0.909
Discontinuation due to AEs (≥ 1 drug component)	193	NA 22 (11.4)	188	NA 17 (9.0)	1.04 [0.54; 2.01]; 0.895
Peripheral neuropathy (HLT, AEs [CTCAE grade ≥ 2])	193	NA 28 (14.5)		NA 20 (10.6)	0.98 [0.54; 1.78]; 0.943

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: daratumumab + VCd versus VCd (multipage table)

Study outcome category outcome	Daratumumab + VCd		VCd		Daratumumab + VCd vs. VCd
	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[b]
Skin and subcutaneous tissue disorders (SOC, AEs)	193	14.85 [6.50; NC] 97 (50.3)	188	NA 42 (22.3)	2.00 [1.37; 2.92]; < 0.001
Hypokalaemia (PT, severe AEs[m])	193	NA 4 (2.1)	188	NA 10 (5.3)	0.27 [0.07; 0.997]; 0.0495

a. Hazard ratio (incl. 95% CI) calculated using the Cox proportional hazard model with the stratification factors cardiac stage at baseline (Mayo stage I vs. Mayo stage II vs. Mayo stage IIIa), countries that typically offer transplantation for patients with AL amyloidosis (list A: yes vs. list B: no), renal function status at baseline (CrCl < 60 mL/min vs. CrCl ≥ 60 mL/min)
b. Log-rank test stratified by cardiac stage at baseline (Mayo stage I vs. Mayo stage II vs. Mayo stage IIIa), countries that typically offer transplantation for patients with AL amyloidosis (list A: yes vs. list B: no), renal function status at baseline (CrCl < 60 mL/min vs. CrCl ≥60 mL/min).
c. Defined as: clinical manifestation of heart failure defined as the need for a heart transplant, a left ventricular assist device (LVAD) or an intra-aortic balloon pump (IABP) and clinical manifestation of renal failure defined as the development of end-stage renal disease (need for haemodialysis or kidney transplantation).
d. Institute's calculation of the percentages.
e. The data in Module 4 A and Module 5 are discrepant; the figures from Module 5 are presented.
f. A score increase by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range 0 to 100).
g. Only those study participants are analysed for which the baseline value and at least one follow-up value are available. Study participants without a baseline or follow-up value are censored at the time of randomization. Contrary to the statistical analysis plan (SAP), patients who have died as a result of disease progression are not categorized as patients with an event.
h. From the disease-specific modules EORTC QLQ-MY20 (tingling in hands and feet), EORTC QLQ-OV28 (feeling of fullness in the abdomen/stomach), EORTC QLQ-PR25 (swelling of the legs or ankles).
i. A score decrease by ≥ 15 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
j. A score decrease by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
k. Module 4 A and Module 5 (additional analyses) provide partially discrepant data on the role functioning scale; the figures from Module 5 are presented.
l. A decrease in PCS by ≥ 9.4 points or in MCS by ≥ 9.6 points from baseline is considered a clinically relevant deterioration (scale range: 7.3 to 70.1 for PCS and 5.8 to 69.9 for MCS; determined using the 2009 norm sample [27]). No responder analyses are available on the SF-36v2 subscales.
m. Operationalized as CTCAE grade ≥ 3.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: daratumumab + VCd versus VCd (multipage table)

Study outcome category outcome	Daratumumab + VCd N	Daratumumab + VCd median time to event in months [95% CI] patients with event n (%)	VCd N	VCd median time to event in months [95% CI] patients with event n (%)	Daratumumab + VCd vs. VCd HR [95% CI][a]; p-value[b]
AE: adverse event; AL: amyloidogenic free light chains; CI: confidence interval; CrCl: creatinine clearance; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HLT: High Level Term; HR: hazard ratio; MY20: Multiple Myeloma 20; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; OV28: Ovarian Cancer 28; PR25: Prostate Cancer 20; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SAP: statistical analysis plan; SF-36: Short Form (36) Health Survey; SOC: System Organ Class; VAS: visual analogue scale; VCd: bortezomib + cyclophosphamide + dexamethasone					

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes (see Section I 3.2).

Mortality

The final data cut-off (15 November 2024) showed a statistically significant difference in favour of daratumumab + VCd for the outcome overall survival. There is thus a hint of an added benefit of daratumumab + VCd over VCd.

Morbidity

Major organ deterioration

For the composite outcome major organ deterioration, consisting of clinical manifestation of heart failure and clinical manifestation of renal failure, there is a statistically significant difference in favour of daratumumab + VCd at the second data cut-off of 17 April 2024. The results are particularly influenced by the component clinical manifestation of renal failure. There is thus a hint of an added benefit of daratumumab + VCd over VCd.

Symptoms

EORTC QLQ-C30

Dyspnoea

For the outcome dyspnoea (recorded with the EORTC QLQ-C30), there was a statistically significant difference in favour of daratumumab + VCd in the analysis of the time to first deterioration at the second data cut-off of 17 April 2024. However, the extent of the effect is

no more than marginal for this outcome. There is no hint of an added benefit of daratumumab + VCd in comparison with VCd; an added benefit is therefore not proven.

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

For each of the outcomes fatigue, nausea and vomiting, pain, insomnia, appetite loss, constipation and diarrhoea (recorded using the EORTC QLQ-C30), there was no statistically significant difference between the treatment groups in the analysis of the time to first deterioration at the second data cut-off of 17 April 2024. In each case, there was no hint of an added benefit of daratumumab + VCd in comparison with VCd; an added benefit is therefore not proven.

EORTC QLQ individual items

Tingling in the hands and feet (EORTC QLQ-MY20), feeling of fullness in the abdomen/stomach (EORTC QLQ-OV28) and swelling of the legs or ankles (EORTC QLQ-PR25)

For each of the outcomes tingling in the hands and feet (EORTC QLQ-MY20), feeling of fullness in the abdomen/stomach (EORTC QLQ-OV28) and swelling of the legs or ankles (EORTC QLQ-PR25), there was no statistically significant difference between the treatment groups in the analysis of the time to first deterioration at the second data cut-off of 17 April 2024. In each case, there was no hint of an added benefit of daratumumab + VCd in comparison with VCd; an added benefit is therefore not proven.

Health status

For health status (recorded using the EQ-5D VAS), there was no statistically significant difference between the treatment groups in the analysis of the time to first deterioration at the second data cut-off of 17 April 2024. There is no hint of an added benefit of daratumumab + VCd in comparison with VCd; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

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

For the outcomes physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning (recorded using the EORTC QLQ-C30), there was no statistically significant difference between the treatment groups in the analysis of the time to first deterioration at the second data cut-off of 17 April 2024. In each case, there was no hint of an added benefit of daratumumab + VCd in comparison with VCd; an added benefit is therefore not proven.

SF-36

For the PCS and the MCS, measured using the SF-36, the analysis of the time to first deterioration showed no statistically significant difference between the treatment arms at the second data cut-off of 17 April 2024. In each case, there was no hint of an added benefit of daratumumab + VCd in comparison with VCd; an added benefit is therefore not proven.

Side effects

SAEs

There was no statistically significant difference between the treatment arms for the outcome SAE at the final data cut-off of 15 November 2024. There is no hint of greater or lesser harm from daratumumab + VCd in comparison with VCd; greater or lesser harm is therefore not proven.

Severe AEs

There was no statistically significant difference between the treatment arms for the outcome severe AEs at the final data cut-off of 15 November 2024. There is no hint of greater or lesser harm from daratumumab + VCd in comparison with VCd; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

There was no statistically significant difference between the treatment arms for the outcome discontinuation due to AEs at the final data cut-off of 15 November 2024. There is no hint of greater or lesser harm from daratumumab + VCd in comparison with VCd; greater or lesser harm is therefore not proven.

Specific AEs

Peripheral neuropathy (AEs)

There was no statistically significant difference between the treatment arms for the outcome peripheral neuropathy (AE) at the final data cut-off of 15 November 2024. There is no hint of greater or lesser harm from daratumumab + VCd in comparison with VCd; greater or lesser harm is therefore not proven.

Skin and subcutaneous tissue disorders (AEs)

The final data cut-off of 15 November 2024 showed a statistically significant difference to the disadvantage of daratumumab + VCd for the outcome skin and subcutaneous tissue disorders (AEs). There is a hint of greater harm from daratumumab + VCd in comparison with VCd.

Hypokalaemia (severe AEs)

The final data cut-off of 15 November 2024 showed a statistically significant difference in favour of daratumumab + VCd for the outcome hypokalaemia (severe AEs). There is a hint of lesser harm from daratumumab + VCd in comparison with VCd.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics were relevant for the present benefit assessment:

- sex (female versus male)
- age (< 65 years versus ≥ 65 years)
- cardiac involvement (yes versus no)

In the present situation, however, the results from the subgroup analyses are not considered interpretable and are not considered further. This is justified below:

The subgroup characteristics considered are factors that are important in the choice of therapy for patients with newly diagnosed AL amyloidosis. In the respective subgroups, for example patients of advanced age or patients with cardiac involvement, there is an additional uncertainty regarding the choice of therapy in addition to the uncertainty already described with regard to the patient population included in the ANDROMEDA study (see Section I 3.2). For example, a 2-drug combination could potentially be indicated as an individualized treatment for some patients of the subgroup ≥ 65 years of age, or treatment with lenalidomide for some of the patients in the subgroup without cardiac involvement [14,19]. For this reason, only the total population of the ANDROMEDA study was considered in this situation.

I 5 Probability and extent of added benefit

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

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

I 5.1 Assessment of added benefit at outcome level

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

Determination of the outcome category for outcomes on symptoms and side effects

For the following symptom outcome(s), it cannot be inferred from the dossier whether they are serious/severe or non-serious/non-severe. The classification of this outcome/these outcomes is justified below.

Symptoms

Dyspnoea (EORTC QLQ-C30)

For the outcome dyspnoea, there is no information available on the assignment of the severity grade that would result in a classification as serious/severe. Therefore, this outcome was assigned to the outcome category of non-serious/non-severe symptoms/late complications. The company itself did not allocate them to any outcome category in its dossier.

Specific AEs

Skin and subcutaneous tissue disorders (AEs)

Only 4 patients with an event in the SOC skin and subcutaneous tissue disorders had a severity level of 3 or 4 according to CTCAE, and only 2 patients had a corresponding SAE. The outcome was therefore assigned to the outcome category of non-serious/non-severe side effects. This concurs with the company’s assessment.

Table 16: Extent of added benefit at outcome level: daratumumab + VCd versus VCd (multipage table)

Outcome category **outcome**	**Daratumumab + VCd vs. VCd** **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 (data cut-off 15 November 2024)		
Overall survival	NA vs. NA HR: 0.62 [0.42; 0.90]; p = 0.011 probability: hint	Outcome category: mortality $0.85 \leq CI_u < 0.95$ added benefit, extent: considerable
Outcomes with shortened observation period		
Morbidity (data cut-off: 17 April 2024)		
Major organ deterioration	NA vs. NA HR: 0.22 [0.06; 0.79]; p = 0.011 probability: hint	Outcome category: serious/severe symptoms/late complications $0.75 \leq CI_u < 0.90$ added benefit, extent: considerable
Symptoms (EORTC QLQ-C30)		
Fatigue	2.14 vs. 1.94 HR: 0.81 [0.63; 1.04]; p = 0.100	Lesser benefit/added benefit not proven
Nausea and vomiting	29.21 vs. 40.80 HR: 0.87 [0.64; 1.19]; p = 0.390	Lesser benefit/added benefit not proven
Pain	3.98 vs. 3.81 HR: 1.09 [0.84; 1.42]; p = 0.516	Lesser benefit/added benefit not proven
Dyspnoea	29.04 vs. 3.81 HR: 0.71 [0.53; 0.97]; p = 0.029	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[c]
Insomnia	4.67 vs. 4.60 HR: 1.00 [0.76; 1.33]; p = 0.984	Lesser benefit/added benefit not proven
Appetite loss	9.27 vs. 5.78 HR: 0.92 [0.69; 1.23]; p = 0.580	Lesser benefit/added benefit not proven
Constipation	NA vs. NA HR: 1.01 [0.75; 1.34]; p = 0.969	Lesser benefit/added benefit not proven

Table 16: Extent of added benefit at outcome level: daratumumab + VCd versus VCd (multipage table)

Outcome category **outcome**	**Daratumumab + VCd vs. VCd** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Diarrhoea	7.85 vs. 6.44 HR: 0.92 [0.68; 1.23]; p = 0.565	Lesser benefit/added benefit not proven
Symptoms (EORTC QLQ individual items)		
Tingling in hands and feet	13.08 vs. 11.07 HR: 0.83 [0.62; 1.13]; p = 0.236	Lesser benefit/added benefit not proven
Feeling of fullness in the abdomen/stomach	3.88 vs. 2.86 HR: 0.89 [0.68; 1.16]; p = 0.382	Lesser benefit/added benefit not proven
Swelling of the legs or ankles	7.20 vs. 4.63 HR: 0.99 [0.74; 1.32]; p = 0.932	Lesser benefit/added benefit not proven
Health status		
EQ-5D VAS	17.61 vs. 6.24 HR: 0.93 [0.68; 1.26]; p = 0.627	Lesser benefit/added benefit not proven
Health-related quality of life (data cut-off: 17 April 2024)		
EORTC QLQ-C30		
Global health status	4.70 vs. 2.89 HR: 0.82 [0.63; 1.08]; p = 0.158	Lesser benefit/added benefit not proven
Physical functioning	4.73 vs. 3.75 HR: 0.86 [0.66; 1.13]; p = 0.279	Lesser benefit/added benefit not proven
Role functioning	2.69 vs. 2.83 HR: 0.88 [0.68; 1.13]; p = 0.315	Lesser benefit/added benefit not proven
Emotional functioning	47.70 vs. 12.22 HR: 0.78 [0.57; 1.08]; p = 0.135	Lesser benefit/added benefit not proven
Cognitive functioning	5.58 vs. 3.81 HR: 0.85 [0.65; 1.11]; p = 0.222	Lesser benefit/added benefit not proven
Social functioning	2.79 vs. 2.86 HR: 1.09 [0.84; 1.41]; p = 0.521	Lesser benefit/added benefit not proven

Table 16: Extent of added benefit at outcome level: daratumumab + VCd versus VCd (multipage table)

Outcome category **outcome**	**Daratumumab + VCd vs. VCd** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
SF-36		
Physical Component Summary (PCS)	64.39 vs. 24.21 HR: 0.77 [0.55; 1.06]; p = 0.106	Lesser benefit/added benefit not proven
Mental Component Summary (MCS)	14.92 vs. 28.62 HR: 1.04 [0.77; 1.42]; p = 0.788	Lesser benefit/added benefit not proven
Side effects (data cut-off: 15 November 2024)		
SAEs	NA vs. NA HR: 1.01 [0.73; 1.41]; p = 0.934	Lesser benefit/added benefit not proven
Severe AEs	3.61 vs. 3.48 HR: 1.01 [0.78; 1.32]; p = 0.909	Lesser benefit/added benefit not proven
Discontinuation due to AEs	NA vs. NA HR: 1.04 [0.54; 2.01]; p = 0.895	Lesser benefit/added benefit not proven
Peripheral neuropathy (AEs)	NA vs. NA HR: 0.98 [0.54; 1.78]; p = 0.943	Lesser benefit/added benefit not proven
Skin and subcutaneous tissue disorders (AEs)	14.85 vs. NA HR: 2.00 [1.37; 2.92] HR: 0.5 [0.34; 0.73][d]; p < 0.001 probability: hint	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ greater harm, extent: “considerable”
Hypokalaemia (severe AEs)	NA vs. NA HR: 0.27 [0.07; 0.997]; p = 0.0495 probability: hint	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ lesser harm, extent: “minor”

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. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
d. Institute’s calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit.

Table 16: Extent of added benefit at outcome level: daratumumab + VCd versus VCd (multipage table)

Outcome category **outcome**	**Daratumumab + VCd vs. VCd** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
AE: adverse events, CI: confidence interval; CI_u: upper limit of the confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; NA: not achieved; QLQ-C30: Quality of Life Questionnaire-Core 30; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; VAS: visual analogue scale; VCd: bortezomib + cyclophosphamide + dexamethasone		

I 5.2 Overall conclusion on added benefit

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

Table 17: Positive and negative effects from the assessment of daratumumab + VCd in comparison with VCd

Positive effects	**Negative effects**
Outcomes with observation over the entire study duration	
Mortality ▪ overall survival: hint of added benefit – extent: “considerable”	–
Outcomes with shortened observation period	
Serious/severe symptoms/late complications ▪ major organ deterioration: hint of added benefit – extent: “considerable”	–
Serious/severe side effects ▪ hypokalaemia (severe AEs): hint of lesser harm – extent: "minor"	–
–	Non-serious/non-severe side effects ▪ skin and subcutaneous tissue disorders (AEs): hint of greater harm – extent: “considerable”
AE: adverse event; VCd: bortezomib + cyclophosphamide + dexamethasone	

All things considered, both positive and negative effects of different extents were found for daratumumab + VCd compared with VCd.

On the positive effects side, there is a hint of considerable added benefit for the outcome overall survival and for the category of severe/serious symptoms. Moreover, there was a hint of lesser harm with the extent "minor" in the category of serious/severe side effects. In the category non-serious/non-severe side effects there is a hint of greater harm with the extent

"considerable". The negative effect with considerable extent in the outcome category of non-serious/non-serious side effects does not challenge the positive effects.

In summary, for patients with newly diagnosed systemic AL amyloidosis for whom VCd is the appropriate therapy for the individual patient, there is a hint of considerable added benefit of daratumumab + VCd compared with the ACT.

Table 18 summarizes the result of the assessment of the added benefit of daratumumab + VCd comparison with the ACT.

Table 18: Daratumumab + VCd – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with newly diagnosed systemic AL amyloidosis for whom VCd is the suitable therapy for the individual patientb	VCd[c]	Hint of considerable added benefit

a. Presented is the ACT specified by the G-BA.
b. This research question arises in differentiation from other options of individualized treatment for newly diagnosed systemic AL amyloidosis (see dossier assessment A21-100 [3]). Apart from daratumumab in combination with VCd, no drug therapies are approved for the treatment of AL amyloidosis. In A21-100, various therapy combinations were considered suitable comparators for individualized therapy, including VCd, as part of a clinical study. The ACT also included high-dose melphalan therapy with subsequent ASCT as part of an individualized treatment for suitable patients. This could be indicated immediately or after completed induction therapy. In principle, the therapeutic indication also covers patients for whom immediate ASCT is an option.
c. Apart from daratumumab in combination with VCd, no other drugs are approved for this indication. According to Section 6 (2) sentence 2 of the Regulation on the AM-NutzenV, the determination of the ACT in this context is to be based on the actual health care situation as it would be without the drug to be assessed. The G-BA points out that the use of VCd is medically necessary. According to the generally recognized state of medical knowledge with regard to the patient group to be assessed, off-label use is considered the therapy standard.

ASCT: autologous stem cell transplantation; AL amyloidosis: light-chain amyloidosis; AM-NutzenV: Regulation for Early Benefit Assessment of New Pharmaceuticals; G-BA: Federal Joint Committee; VCd: bortezomib + cyclophosphamide + dexamethasone

The assessment described above differs from that of the company, which derived an indication of considerable added benefit for adults with newly diagnosed systemic AL amyloidosis for whom VCd is the most suitable therapy for the individual patient.

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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