IQWiG Reports – Commission No. A21-100

Daratumumab (systemic light-chain amyloidosis) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Daratumumab (systemische Leichtketten-Amyloidose) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 October 2021). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ASCT	autologous stem cell transplantation
AL	amyloid light chain
CHR	complete haematological response
CTCAE	Common Terminology Criteria for Adverse Events
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EORTC QLQ-MY20	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Multiple Myeloma 20
EORTC QLQ-OV28	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Ovarian Cancer 28
EORTC QLQ-PR25	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Prostate Cancer 25
EQ-5D	European Quality of Life 5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HLT	high level term
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MCS	Mental Component Summary
MOD-PFS	major organ deterioration – progression-free survival
NYHA	New York Heart Association
PCS	Physical Component Summary
PT	preferred term
RCT	randomized controlled trial
SAE	serious adverse event
SF-36	Short Form-36
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
VAS	visual analogue scale
VCd	cyclophosphamide, bortezomib, and dexamethasone

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug daratumumab (in combination with cyclophosphamide, bortezomib, and dexamethasone [VCd]). The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 27 July 2021.

Research question

The aim of this report is to assess the added benefit of daratumumab in combination with VCd in comparison with the appropriate comparator therapy (ACT) for adult patients with newly diagnosed systemic amyloid light-chain amyloidosis (AL amyloidosis).

The G-BA's specification of the ACT results in the research question presented in Table 2.

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

Therapeutic indication	**ACT**[a]
Treatment of adult patients with newly diagnosed systemic light-chain amyloidosis[b]	Individualized therapy, taking into account general health, comorbidity, and organ deterioration[c]

a. Presented is the ACT specified by the G-BA.
b. In principle, the therapeutic indication includes patients eligible for immediate stem cell transplantation.
c. No drug therapies have been approved for the treatment of light-chain amyloidosis. For individualized therapy, the following therapies are deemed suitable comparators within clinical trials: bortezomib + cyclophosphamide + dexamethasone, bortezomib ± dexamethasone, bortezomib + melphalan + dexamethasone, lenalidomide + cyclophosphamide + dexamethasone, lenalidomide + dexamethasone, melphalan + dexamethasone, lenalidomide + melphalan + dexamethasone. As part of individualized therapy for eligible patients, the ACT also includes high-dose melphalan therapy with subsequent autologous stem cell transplantation. The latter may be indicated either immediately or following induction therapy.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; VCd: bortezomib + cyclophosphamide + dexamethasone

The company had initially followed the specified ACT, but subsequently claimed to present data on the comparison with VCd. The company's approach remains without consequences regarding the identification of relevant studies since, in its information procurement, the company took into account all treatment options of individualized therapy listed by the G-BA in the notes on the ACT and the check of completeness of the study pool did not show any relevant studies comparing with another treatment option listed by the G-BA. Performing a comparison versus VCd based on the available study pool, the benefit assessment determined the extent to which conclusions regarding a subpopulation (the group of patients for which VCd is individually best suited) can be derived.

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

Study pool and study design

The ANDROMEDA study was used for the benefit assessment. The ANDROMEDA study is an open-label RCT comparing daratumumab + VCd versus VCd. The study included adult patients with newly diagnosed systemic AL amyloidosis. Alongside a histopathological diagnosis, patients had to exhibit measurable disease defined by exceeding defined thresholds of serum M protein and/or free light chains in serum. Patients were to have 1 or more organs impacted by AL amyloidosis and Eastern Cooperative Oncology Group Performance Status (ECOG-PS) ≤ 2. Patients with evidence of significant cardiovascular conditions, e.g. New York Heart Association (NYHA) classification IIIb or IV heart failure, or with planned autologous stem cell transplantation (ASCT) during the first 6 cycles of therapy were excluded from the study.

A total of 388 patients were randomized in a 1:1 ratio to treatment with daratumumab + VCd (N = 195) or VCd (N = 193).

In both treatment arms, the study medication was administered in 28-day cycles. Patients in the intervention arm received daratumumab + VCd in the first 6 cycles and daratumumab monotherapy from Cycle 7 to a maximum of 24 cycles. Patients in the comparator arm received a maximum of 6 VCd cycles. Treatment with daratumumab+VCd was administered subcutaneously in accordance with the Summary of Product Characteristics (SPC). VCd treatment in the ANDROMEDA comparator arm was administered at the same VCd dose as in the intervention arm. Patients were treated until either disease progression, start of follow-up therapy, unacceptable toxicity, or withdrawal of consent.

Primary outcome of the study was complete haematological response (CHR). Patient-relevant secondary outcomes were overall survival and outcomes on morbidity, health-related quality of life, and adverse events (AEs).

The 14 February 2020 data cut-off presented in this benefit assessment had been prespecified and was to take place when all patients had received at least 6 treatment cycles. It ended up being taken at about 6 months after inclusion of the last patient.

Implementation of the ACT

The G-BA specified the ACT as individualized therapy, taking into account general health status, comorbidity, and organ deterioration; it also listed suitable comparators for use in clinical trials in the comments on the ACT. The ANDROMEDA comparator arm used only VCd. No multi-comparator study comparing multiple treatment options is available.

Bortezomib is generally a treatment option for the study population since the ANDROMEDA study excluded patients with grade 2 sensory peripheral neuropathy or grade 1 painful peripheral neuropathy and as per bortezomib SPC, patiens with prior severe neuropathy should receive bortezomib treatment only following a thorough benefit-risk assessment. For patients not contraindicated for bortezomib, current guidelines further specify bortezomib-containing combinations as standard therapy, with VCd being the currently preferred combination for patients with newly diagnosed systemic AL amyloidosis. In contrast, combinations of only 2 drugs, e.g. bortezomib or melphalan + dexamethasone, tend to be recommended for older, fragile patients or patients at high risk of complications and treatment-related mortality. Overall, most patients in the ANDROMEDA study can be assumed to be in good general health. Hence, it can be assumed that the VCd triple combination is the suitable therapy for the majority of patients in the ANDROMEDA study. In the ANDROMEDA study population, melphalan-based and lenalidomide-based therapy is deemed of low importance.

Overall, for the ANDROMEDA study population, the VCd treatment combination is deemed an adequate implementation of individualized therapy, taking into account general health, comorbidity, and organ deterioration. Based on the ANDROMEDA study, however, conclusions can be drawn only on the added benefit of daratumumab + VCd in comparison with individualized therapy for the group of patients for whom VCd represents the individually best suited therapy. However, the certainty of results of all outcomes was reduced since the percentage of ANDROMEDA study participants for whom therapy other than VCd represents the most suitable individualized therapy is unknown – albeit low.

Risk of bias and certainty of results

The risk of bias across outcomes was rated as low in the ANDROMEDA study. At the outcome level, the risk of bias of results was rated as high for each of the outcomes, except overall survival. Since the certainty of results is reduced due to the uncertainty in the implementation of individualized therapy in the ANDROMEDA study (VCd), at most hints can be derived for all outcomes.

Results

Time-to-event analyses are used for all outcomes.

Mortality

Overall survival

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

Morbidity

Major organ deterioration

For the outcome of major organ deterioration, a statistically significant difference was found in favour of daratumumab + VCd. This results in a hint of added benefit of daratumumab + VCd in comparison with VCd.

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

Time to deterioration by ≥ 10 points was used.

Dyspnoea

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

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

No statistically significant difference between treatment arms was found for any of the outcomes of fatigue, nausea and vomiting, pain, insomnia, appetite loss, constipation, or diarrhoea. Consequently, there was no hint of added benefit of daratumumab + VCd in comparison with VCd for any of them; an added benefit is therefore not proven.

Health status (visual analogue scale [VAS] of European Quality of Life 5 Dimensions [EQ-5D])

Time to deterioration by ≥ 15 points was used.

For the outcome of health status, as recorded with the EQ-5D VAS, no statistically significant difference between treatment groups was found. There was therefore no hint of added benefit of daratumumab + VCd in comparison with VCd; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

Time to deterioration by ≥ 10 points was used.

Emotional functioning

For the outcome of emotional functioning, a statistically significant difference was found in favour of daratumumab + VCd. This results in a hint of added benefit of daratumumab + VCd in comparison with VCd.

Physical functioning, role functioning, cognitive functioning, social functioning, global health status

No statistically significant difference between treatment groups was found for any of the outcomes of physical functioning, role functioning, cognitive functioning, social functioning,

and global health status. Consequently, there was no hint of added benefit of daratumumab + VCd in comparison with VCd for any of them; an added benefit is therefore not proven.

Short Form-36 Health Survey (SF-36)

For the Physical Component Summary (PCS) and Mental Component Summary (MCS), time to deterioration by ≥ 10.80 points (MCS) or ≥ 10.05 (PCS) was used.

No statistically significant difference between treatment groups was found for either PCS or MCS. Consequently, there was no hint of added benefit of daratumumab + VCd in comparison with VCd for any of them; an added benefit is therefore not proven.

Side effects

Regarding the interpretation of side effects results, it must be noted that, due to the much shorter planned treatment duration and the associated discontinuation of follow-ups in the comparator arm, the hazard ratio reflects a comparison covering only the first 7 months after randomization.

Serious AEs (SAEs), severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade 3–4) and discontinuation due to AEs (≥ 1 drug component)

No statistically significant difference between treatment groups was found for any of the outcomes of SAEs, severe AEs (CTCAE ≥ grade 3), or discontinuation due to AEs (≥ 1 drug component). Consequently, no hint of greater or lesser harm from daratumumab + VCd in comparison with VCd can be derived for any of them; greater or lesser harm is therefore not proven.

Peripheral neuropathies (high level term [HLT], AEs)

No usable data were available on the outcome of peripheral neuropathies (HLT, AEs). Consequently, no hint of greater or lesser harm from daratumumab + VCd in comparison with VCd can be derived for any of them; greater or lesser harm is therefore not proven.

Skin and subcutaneous tissue disorders (system organ class [SOC], AEs)

For the outcome of skin and subcutaneous tissue disorders (SOC, AEs), a statistically significant difference was found to the disadvantage of daratumumab + VCd. This results in a hint of greater benefit of daratumumab + VCd in comparison with VCd.

Hypokalaemia (preferred term [PT], severe AEs [CTCAE grade ≥ 3])

For the outcome of hypokalaemia (PT, severe AEs [CTCAE grade ≥ 3]), a statistically significant difference was found in favour of daratumumab + VCd. This results in a hint of lesser harm of 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 extent of added benefit of the drug daratumumab plus VCd in comparison with the ACT are assessed as follows:

On the basis of the ANDROMEDA study, conclusions can be drawn only on patients for whom VCd is the best suited ACT. No data are available on patients for whom treatment other than VCd is the best suited ACT. Therefore, added benefit is derived separately for these two patient groups.

Patients for whom VCd is the best suited ACT

Overall, several favourable effects in the outcome categories of serious/severe symptoms / late complications, non-serious/non-severe symptoms / late complications, health-related quality of life, and serious/severe side effects counteract one unfavourable effect in the outcome category of non-serious/non-severe side effects. The favourable effects are of minor extent. The unfavourable effect of considerable extent in the outcome category of non-serious/non-severe side effects does not call the favourable effects into question. In summary, for adult patients with newly diagnosed AL amyloidosis for whom VCd is the best suited ACT, a hint of minor added benefit of daratumumab was found in comparison with individualized therapy, taking into account general health, comorbidity, and organ deterioration.

Patients for whom a therapy other than VCd is the best suited ACT

The company did not present any data on adult patients with newly diagnosed systemic AL amyloidosis for whom a therapy other than VCd is the best suited ACT. For these patients, there is consequently no hint of added benefit of daratumumab in comparison with individualized therapy, taking into account general health, comorbidity, and organ deterioration; added benefit is therefore not proven.

Table 3 presents a summary of the probability and extent of added benefit of daratumumab + 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: Daratumumab + VCd – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Treatment of adult patients with newly diagnosed systemic light-chain amyloidosis[b]	Individualized therapy, taking into account general health, comorbidity, and organ deterioration[c]	Patients for whom bortezomib + cyclophosphamide + dexamethasone is best suited: Hint of minor added benefit
		Patients for whom a therapy other than bortezomib + cyclophosphamide + dexamethasone is best suited: Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. In principle, the therapeutic indication includes patients eligible for immediate stem cell transplantation.
c. No drug therapies have been approved for the treatment of light-chain amyloidosis. For individualized therapy, the following therapies are deemed suitable comparators within clinical trials: bortezomib + cyclophosphamide + dexamethasone, bortezomib ± dexamethasone, bortezomib + melphalan + dexamethasone, lenalidomide + cyclophosphamide + dexamethasone, lenalidomide + dexamethasone, melphalan + dexamethasone, lenalidomide + melphalan + dexamethasone. As part of individualized therapy for eligible patients, the ACT also includes, high-dose melphalan therapy with subsequent autologous stem cell transplantation. The latter can be indicated either immediately or following induction therapy.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; VCd: bortezomib + cyclophosphamide + dexamethasone

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

2.2 Research question

The aim of this report is to assess the added benefit of daratumumab in combination with VCd in comparison with the ACT for adult patients with newly diagnosed systemic light-chain amyloidosis (AL amyloidosis).

The G-BA's specification of the ACT results in the research question presented in Table 4.

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

Therapeutic indication	**ACT[a]**
Treatment of adult patients with newly diagnosed systemic light-chain amyloidosis[b]	Individualized therapy, taking into account general health, comorbidity, and organ deterioration[c]

a. Presented is the ACT specified by the G-BA.
b. In principle, the therapeutic indication includes patients eligible for immediate stem cell transplantation.
c. No drug therapies have been approved for the treatment of light-chain amyloidosis. For individualized therapy, the following therapies are deemed suitable comparators within clinical trials: bortezomib + cyclophosphamide + dexamethasone, bortezomib ± dexamethasone, bortezomib + melphalan + dexamethasone, lenalidomide + cyclophosphamide + dexamethasone, lenalidomide + dexamethasone, melphalan + dexamethasone, lenalidomide + melphalan + dexamethasone. As part of individualized therapy for eligible patients, the ACT also includes high-dose melphalan therapy with subsequent autologous stem cell transplantation. The latter can be indicated either immediately or following induction therapy.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; VCd: bortezomib + cyclophosphamide + dexamethasone

The company had initially followed the specified ACT, but subsequently claimed to present data on the comparison with VCd. The company's approach remains without consequences regarding the identification of relevant studies since, in its information procurement, the company took into account all treatment options of individualized therapy listed by the G-BA in the notes on the ACT and the check of completeness of the study pool did not show any relevant studies comparing with another treatment option listed by the G-BA. Performing a comparison versus VCd based on the available study pool, the benefit assessment determined the extent to which conclusions regarding a subpopulation (the group of patients for which VCd is individually best suited) can be derived.

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

2.3 Information retrieval and study pool

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

Sources cited by the company in the dossier:

- Study list on daratumumab (status: 3 June 2021)
- Bibliographic literature search on daratumumab (most recent search on 2 June 2021)

- Search in trial registries / study results databases on daratumumab (most recent search on 29 June 2021)
- Search on the G-BA website on daratumumab (most recent search on 16 June 2021)

To check the completeness of the study pool:

- Search in trial registries for daratumumab (most recent search on 11 August 2021); see Appendix A of the full dossier assessment for search strategies.

The check did not identify any additional relevant studies.

2.3.1 Included studies

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

Table 5: Study pool – RCT, direct comparison: Daratumumab + VCd vs. VCd

Study	Study category			Available sources		
	Approval study for the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (yes/no [reference])	Registry entries[b] (yes/no [reference])	Publication (yes/no [reference])
54767414AMY3001, (ANDROMEDA[c])	Yes	Yes	No	Yes [3,4]	Yes [5,6]	Yes [7]

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

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; RCT: randomized controlled trial; VCd: bortezomib + cyclophosphamide + dexamethasone

The study pool matches that used by the company. In the ANDROMEDA study, daratumumab + VCd was compared with VCd; therefore, this study is suitable for drawing conclusions on the added benefit of daratumumab + VCd only for the group of patients for whom VCd represents the best suited individualized therapy. No data are available on patients for whom different treatment options are better suited.

2.3.2 Study characteristics

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

Table 6: Characterization of the included study – RCT, direct comparison: daratumumab + VCd vs. VCd (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and time period conducted	Primary outcome; secondary outcomes[a]
ANDROMEDA	RCT[b], open-label, parallel-group	Adults (≥ 18 years) with newly diagnosed systemic light-chain amyloidosis[c] and ▪ ≥ 1 organ affected by amyloidosis[d] ▪ Without significant cardiovascular conditions[e] ▪ Without planned ASCT within the first 6 treatment cycles ▪ ECOG-PS ≤ 2	Daratumumab + VCd (N = 195) VCd (N = 193)	Screening: 28 days Treatment: ▪ daratumumab: maximum of 24 cycles ▪ VCd (in both study arms): maximum of 6 cycles Or until either disease progression, start of subsequent therapy, unacceptable toxicity, or withdrawal of consent Follow-up: outcome-specific[f], maximum until death Data cut-off dates: 14 February 2020[g] 15 June 2020[h]	A total of 140 centres in Australia, Belgium, Brazil, Canada, China, Denmark, Germany, France, Greece, Hungary, Israel, Italy, Japan, Mexico, Netherlands, Poland, Sweden, Spain, South Korea, Turkey, United Kingdom, United States 10/2017 – ongoing	Primary: CHR total response rate Secondary: overall survival, symptoms, health status, health-related quality of life, AEs

Table 6: Characterization of the included study – RCT, direct comparison: daratumumab + VCd vs. VCd (multipage table)

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

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. Before randomization, a single-arm run-in phase was conducted for assessing the safety profile of daratumumab + VCd.
c. In addition to a histopathological diagnosis, patients had to exhibit measurable disease, as defined by ≥ 1 of the following criteria: serum M protein ≥ 0.5 g/dL by protein electrophoresis (routine serum protein electrophoresis and immunofixation electrophoresis performed at a central laboratory) and/or free light chain in serum ≥ 50 mg/L with an abnormal kappa:lambda ratio or the difference between involved and uninvolved free light chains (dFLC) ≥ 50mg/L.
d. Definition of organ involvement as per NCCN Guidelines for Systemic Light-Chain Amyloidosis [8].
e. NT-ProBNP > 8500 ng/L; NYHA classification IIIb or IV heart failure; heart failure which, in the opinion of the investigator, is on the basis of ischaemic heart disease or uncorrected valvular disease and not primarily due to amyloid cardiomyopathy; inpatient admission to a hospital for unstable angina or myocardial infarction within the 6 months prior to the first dose or percutaneous cardiac intervention with recent stent or coronary artery bypass grafting within 6 months; for participants with heart failure: cardiovascular-related hospitalizations ≤ 4 weeks prior to randomization; participants with a history of sustained ventricular tachycardia or aborted ventricular fibrillation or with a history of AV nodal or SA nodal dysfunction for whom a pacemaker or implantable cardioverter-defibrillator was indicated, but not placed; at screening: 12-lead ECG showing a baseline QTcF > 500 ms; supine systolic blood pressure < 90 mmHg, or symptomatic orthostatic hypotension.
f. Outcome-specific data are provided in Table 8.
g. Prespecified data cut-off approx. 6 months after inclusion of the last patient.
h. From120-day safety data cut-off; corresponds to an FDA-requested safety update 4 months after the 1st data cut-off.

AE: adverse event; ASCT: autologous stem cell transplantation; AV: atrioventricular; CHR: complete haematological response; ECG: electrocardiogram; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; FDA: Food and Drug Administration; Hg: mercury; N: number of randomized patients; NCCN: National Comprehensive Cancer Network; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; NYHA: New York Heart Association; QTcF: QT interval as corrected by Fridericia's formula; RCT: randomized controlled trial; SA: sinoatrial; VCd: bortezomib + cyclophosphamide + dexamethasone

Table 7: Characterization of the intervention – RCT, direct comparison: daratumumab + VCd vs. VCd (multipage table)

Study	Intervention	Comparison
ANDROMEDA	Daratumumab 1800 mg, s. c. ▪ Cycles 1–2: weekly (Days 1, 8, 15, 22) ▪ Cycles 3–6: every 2 weeks (Days 1, 15) ▪ From Cycle 7: every 4 weeks (Day 1) +	
	Bortezomib 1.3 mg/m² BSA, s.c.[a] ▪ Cycles 1–6: weekly (Days 1, 8, 15, 22) +	Bortezomib 1.3 mg/m² BSA, s.c.[a] ▪ Cycles 1–6: weekly (Days 1, 8, 15, 22) +
	Cyclophosphamide 300 mg/m² BSA[b], orally or i.v. ▪ Cycles 1–6: weekly (Days 1, 8, 15, 22) +	Cyclophosphamide 300 mg/m² BSA[b], orally or i.v. ▪ Cycles 1–6: weekly (Days 1, 8, 15, 22) +
	Dexamethasone[c] 40 mg[d, e], i.v. or orally ▪ Cycles 1–6: weekly (Days 1, 8, 15, 22) Cycle duration: 28 days	Dexamethasone[c] 40 mg[d, e], i.v. or orally ▪ Cycles 1–6: weekly (Days 1, 8, 15, 22) Cycle duration: 28 days
	Dose adjustments / treatment discontinuations ▪ Daratumumab; no dose changes allowed; treatment discontinuations due to toxicity allowed for up to 28 days in Cycles 1–6 and up to 6 weeks from Cycle 7 and later. ▪ Bortezomib: 2 dose reductions due to toxicity allowed (1st reduction to 1.0 mg/m² BSA, 2nd reduction to 0.7 mg/m² BSA) ▪ Cyclophosphamide: dose reduction by 50% in case of neutrophil counts 1500–1000/mm³ and/or platelet counts 50 000–100 000/µL; treatment discontinuation at neutrophil counts < 1000/mm³ and/or platelet counts < 50 000/µL. ▪ Dexamethasone: dose reductions allowed upon the investigator's discretion	
	Premedication before daratumumab ▪ 1–3 hours before the administration of daratumumab: paracetamol, antihistamine, dexamethasone[c] ▪ Optionally in Cycle 1, Day 1 up to 24 hours before the administration of daratumumab: montelukast or equivalent **Postmedication before daratumumab** ▪ To be considered on the day after daratumumab administration: low-dose oral methylprednisolone (≤ 20 mg) or equivalent[f] ▪ For patients at increased risk of respiratory complications, the following drugs should be considered after the infusion: antihistamines, leukotriene inhibitors, short-acting beta-2 sympathomimetics, medications controlling the respective lung disease (e.g. inhaled corticosteroids)	

Table 7: Characterization of the intervention – RCT, direct comparison: daratumumab + VCd vs. VCd (multipage table)

Study	Intervention	Comparison
	Nonpermitted prior treatment ▪ Any therapies for treating light-chain amyloidosis or multiple myeloma including drugs targeting CD38 ▪ Strong CYP3A4 inducers < 5 half lives before the 1st dose of the study drug **Concomitant treatment allowed** ▪ All drugs deemed necessary for supportive treatment (except disallowed concomitant treatment; see below) **Recommended** ▪ Infection prevention (pneumocystis-pneumonia prophylaxis; herpes zoster prophylaxis; hepatitis B prophylaxis) ▪ Prophylaxis and therapy of haemorrhagic cystitis ▪ Management of peripheral and pulmonary oedema and heart failure **Disallowed within the first 6 cycles** ▪ Other therapies for treating light-chain amyloidosis, including drugs targeting CD38 ▪ Additional administration of corticosteroids[g] ▪ Other investigatioal substances ▪ Strong CYP3A4 inducers in case of administration of bortezomib	

a. In case of injection-related side effects, bortezomib administration in the form of an infusion was also allowed.
b. At most 500 mg/week irrespective of body surface area.
c. Substitution by an equivalent drug as per local standards allowed.
d. On days without daratumumab administration (for intervention and comparator arm): 40 mg on 1 day or soread over 2 days; on days with daratumumab administration: 20 mg as premedication for daratumumab + 20 mg on the day after daratumumab administration.
e. In patients aged > 70 years, with BMI < 18.5, hypovolaemia, poorly controlled diabetes mellitus, or intolerances/AEs related to prior steroid therapy, a dose of 20 mg was possible (in the intervention arm, as premedication on the days with daratumumab administration).
f. If no infusion-related side effects occurred, postmedication with corticosteroids was administered from Cycle 7 at the investigator's discretion.
g. Exception: patients on long-term steroid treatment (≤ 20 mg/day or equivalent) due to other diseases.

AE: adverse event; BMI: body mass index; BSA: body surface area; CD: cluster of differentiation; COPD: chronic obstructive pulmonary disease; CYP3A4: cytochrome P450 3A4; i.v.: intravenous; RCT: randomized controlled trial; s.c.: subcutaneous; VCd: bortezomib + cyclophosphamide + dexamethasone

The ANDROMEDA study is an ongoing, open-label RCT comparing daratumumab + VCd versus VCd. The study included adult patients with newly diagnosed systemic AL amyloidosis. In addition to a histopathological diagnosis, patients had to have measurable disease, defined by the violation of defined thresholds of serum M protein and/or free light chains in serum (see Table 6). Patients were to have 1 or more organ impacted by AL amyloidosis and an ECOG-PS ≥ 2. Patients with significant cardiovascular conditions such as NYHA classification IIb or IV heart failure as well as planned ASCT within the first 6 cycles of treatment were excluded from study participation.

A total of 388 patients were randomized to treatment with daratumumab + VCd (N = 195) or VCd (N = 193) in a 1:1 ratio. Randomization was stratified by cardiac stage (Mayo stage I

versus II versus IIIa), by countries typically offering stem cell transplantation for patients with AL amyloidosis (list A: yes versus list B: no) and renal function status (creatinine clearance: < 60 mL/min versus ≥ 60 mL/min). The following countries were defined as countries typically offering stem cell transplantation for patients with AL amyloidosis: Australia, Brazil, Canada, Germany, Hungary, Italy, Japan, Netherlands, Poland, Romania, South Korea, Spain, Sweden, Turkey, United Kingdom, and United States. The following countries were defined as countries typically not offering stem cell transplantation: Belgium, China, Denmark, France, Greece, Israel, Mexico.

In both treatment arms, the study medication was administered in 28-day cycles. Patients in the intervention arm received daratumumab + VCd in the first 6 cycles and daratumumab monotherapy starting from Cycle 7 for up to 24 cycles. Patients in the comparator arm received a maximum of 6 cycles of VCd. Daratumumab + VCd was administered subcutaneously as per SPC [9]. VCd treatment in the ANDROMEDA comparator arm was the same as VCd administration in the intervention arm. Patients were treated until either disease progression, start of follow-up therapy, unacceptable toxicity, or withdrawal of consent. Subsequent therapies, including daratumumab therapy, were allowed without restrictions.

Primary outcome of the study was CHR. Patient-relevant secondary outcomes were overall survival and outcomes on morbidity, health-related quality of life, and AEs.

Implementation of the ACT

As the ACT, the G-BA specified individualized therapy, taking into account general health, comorbidities, and organ deterioration. In its comments on the ACT, the G-BA explained that no drugs therapies have been approved for the treatment of AL amyloidosis, but various combination therapies have been mentioned in guidelines and by medical societies and are deemed suitable comparators within clinical trials. They comprise: VCd, bortezomib ± dexamethasone, bortezomib + melphalan + dexamethasone, lenalidomide + cyclophosphamide + dexamethasone, lenalidomide + dexamethasone, melphalan + dexamethasone, and lenalidomide + melphalan + dexamethasone. For eligible patients, the ACT also includes high-dose melphalan therapy (immediately or following induction therapy) with subsequent ASCT within the framework of individualized therapy.

The ANDROMEDA comparator arm used only VCd. No multi-comparator study comparing multiple treatment options is available. Nevertheless, the ANDROMEDA study is suitable for deriving conclusions on added benefit in comparison with individualized therapy, taking into account general health, comorbidity, and organ deterioration for the subpopulation of patients for whom VCd is best suited. The reasoning is provided below.

Bortezomib-containing therapies

As per bortezomib SPC, patients with preexisting severe neuropathy are to receive bortezomib treatment only after a thorough benefit-risk assessment [10]. The ANDROMEDA study excluded patients with grade 2 sensory or grade 1 painful peripheral neuropathy. Hence,

bortezomib is generally a treatment option for the study population. For patients not contraindicated for bortezomib, bortezomib-containing combinations additionally represent the standard treatment in the therapeutic indication as per current guidelines [11-14], with VCd representing the currently preferred combination in patients with newly diagnosed systemic AL amyloidosis [12,13,15]. Combinations with only 2 drugs such as bortezomib or melphalan + dexamethasone, however, tend to be recommended for older, fragile patients or patients at high risk of complications and treatment-related mortality (e.g. NT-proBNP > 8500 ng/L, NYHA stage ≥ III) [12,16]. Presumably, most patients in the ANDROMEDA study are in good general health (8% with ECOG-PS = 2 in the comparator arm; exclusion of patients with NT-proBNP > 8500 ng/L or with other significant cardiovascular conditions; 5% in NYHA stage IIIa in the comparator arm). Hence, the VCd triple combination can be assumed to be the suitable therapy for the majority of individual patients of the ANDROMEDA study.

Melphalan and lenalidomide-containing therapies

For patients who are to receive high-dose melphalan therapy with subsequent ASCT, bortezomib-based therapies represent standard induction therapy [11,14]. Melphalan-based therapies are not recommended for these patients. The same applies to patients for whom ASCT is not an option at present, but has not been ruled out for the future [17]. Accordingly, the G-BA's comments on the ACT state that patients for whom ASCT might be an option in the future should not receive melphalan-based induction therapy. Since most patients included in the ANDROMEDA study were in good general health, however, it can be assumed that for a substantial percentage of patients, ASCT is generally an option and hence melphalan-based therapy is not indicated for first-line therapy. Excluded from study participation were only patients with planned ASCT within the first 6 treatment cycles. All in all, the importance of melphalan-based therapy is therefore deemed low in the ANDROMEDA study population. The same applies to lenalidomide-containing treatment regimen since lenalidomide is primarily recommended if bortezomib is contraindicated [11]. Furthermore, lenalidomide is not recommended in case of AL amyloidosis with cardiac involvement [12,13,18] (71% of patients in the ANDROMEDA comparator arm had cardiac involvement), and as per SPC, it is to be used with caution in case of renal failure [19] (32% of patients in the ANDROMEDA comparator arm were in renal failure stage ≥ III).

Uncertainty regarding the implementation of the ACT

The implementation of the ACT in the ANDROMEDA study is associated with the following uncertainties regarding the option of ASCT, which is included with the ACT: The ANDROMEDA study is also being conducted in countries which typically do not offer stem cell transplantation for patients with AL amyloidosis (see above). In total, 24% of patients in the ANDROMEDA comparator arm were included in such countries. It remains unclear how many of these patients would have been eligible for high-dose melphalan therapy with subsequent ASCT as individualized therapy in the context of the ACT. The group of patients generally eligible for ASCT comprises both patients for whom immediate high-dose melphalan therapy with subsequent ASCT (without induction therapy) is an option as well as those who

received prior induction therapy. In the ANDROMEDA study, the VCd combination administered in the comparator arm is deemed induction therapy in those cases. Overall, the percentage of patients for whom ASCT would have been a suitable ACT, but who did not receive this therapy due to the availability of this health service is deemed low relative to the total population of the ANDROMEDA study.

Another uncertainty regarding the implementation of the ACT is due to the percentage of patients in the ANDROMEDA study who have a translocation t(11:14) in the clonal plasma cell. For this translocation, poorer treatment response has been described under bortezomib [11,12,17]. However, the ANDROMEDA study determined translocation status for only 202 of 388 patients (52%) of the total study population. In the comparator arm, 55 patients (51% of patients in whom the genetic status has been determined) had such a translocation. It is unclear to what extent this affects the general suitability of a bortezomib-containing treatment regimen for these patients.

Summary

Despite the described uncertainties, VCd combination therapy is overall deemed a sufficient implementation of individualized therapy, taking into account general health, comorbidity, and organ deterioration, for the ANDROMEDA study population. Based on the ANDROMEDA study, however, conclusions can be drawn on added benefit of daratumumab + VCd in comparison with individualized therapy, taking into account general health, comorbidity, and organ deterioration only for the subpopulation of patients for whom VCd is best suited. The certainty of results is reduced for all outcomes due to the uncertainty of the, albeit small, percentage of ANDROMEDA study participants for whom a therapy other than VCd is best suited. For all outcomes, at most hints, e.g. of added benefit, can therefore be derived on the basis of the effects demonstrated by the ANDROMEDA study.

The evaluation of the implementation of the ACT in the ANDROMEDA study is generally consistent with that expressed by the company, whose dossier includes an examination as to whether included patients are individually suited for VCd therapy. The company concludes that the ANDROMEDA patient population with newly diagnosed systemic AL amyloidosis can be used to draw conclusions on the added benefit for the patient population suited for VCd treatment, taking into account general health, comorbidity, and organ deterioration (see Section 2.5.2).

Data cut-off

The ANDROMEDA study started in October 2017 and had not yet been completed at the time this benefit assessment was written. The 14 February 2020 data cut-off presented in this benefit assessment had been prespecified and was to take place when all patients had received at least 6 treatment cycles. It ended up being taken at about 6 months after inclusion of the last patient.

Furthermore, a cut-off as per 15 June 2020 exists with respect to side effects for the ANDROMEDA study; this cut-off was requested as a safety update by the Food and Drug

Administration (FDA). Rather than presenting the results as per this data cut-off, Module 4 A of the company's dossier uses the 14 February 2020 data cut-off for all outcomes. In the present situation, the company's decision to use the 14 February 2020 data cut-off for all outcomes is plausible and adequate as per the specifications in the dossier template since the later data cut-off adds very few AE outcome events and took place very soon after the previous data cut-off.

The final analysis of overall survival is planned to take place after 156 events. At the time of the present data cut-off, 56 events had occurred. The study has been planned to end 5 years after randomization of the last patient.

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

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

Study **Outcome category** **Outcome**	**Planned follow-up observation**
ANDROMEDA	
Mortality	
Overall survival	Until death
Morbidity	
Major organ deterioration	Until occurrence of the outcome of MOD-PFS[a, b]
Symptoms / health status (EORTC-QLQ-C30 symptom scales, EQ-5D-VAS)	Until 32 weeks after occurrence of the outcome of MOD-PFS[a]
Health-related quality of life (EORTC-QLQ-C30, SF-36)	Until 32 weeks after occurrence of the outcome of MOD-PFS[a]
Side effects	
All outcomes of the side effects category	Until 30 days after the last dose of study drug or start of a subsequent therapy

a. The combined outcome of MOD-PFS has been reached with occurrence of major organ deterioration (for operationalization, see Section 2.4.1), haematologic progression, or death, whichever is first.
b. Data are available on the planned follow-up duration only for the combined outcome of MOD-PFS. The planned follow-up duration for the component of major organ deterioration is assumed to be in agreement with the combined 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 follow-up times are systematically shortened for all outcomes except for overall survival. Side effects were surveyed only for the period of treatment with the study drug (plus 30 days or up to the start of subsequent therapy). Outcomes on morbidity and health-related quality of life were followed up beyond the treatment period, specifically up to disease progression and

beyond (up to 32 weeks after occurrence of the outcome of major organ deterioration – progression-free survival [MOD-PFS]; see Section 2.4.1 on the definition of the outcome).

To be able to draw a robust conclusion for the entire study period or until patient death, all outcomes – like survival – would have to be surveyed and analysed over the entire period.

Table 9 shows the patient characteristics of the included study.

Table 9: Characterization of the study population – 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
Ancestry, 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 light-chain amyloidosis, n (%)[d]		
Lambda	158 (81)	149 (77)
Kappa	37 (19)	44 (23)
Period 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 (28)
Number of involved organs, 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)
Cardiac stage[e], n (%)		
Stage I	47 (24)	43 (22)
Stage II	76 (39)	80 (41)
Stage IIIa	70 (36)	64 (33)

Table 9: Characterization of the study population – RCT, direct comparison: Daratumumab + VCd vs. VCd (multipage table)

Study Characteristic Category	Daratumumab + VCd N[a] = 195	VCd N[a] = 193
Stage IIIb	2 (1)	6 (3)
NYHA stage, n (%)		
Stage I	101 (52)	94 (49)
Stage II	77 (39)	89 (46)
Stage IIIa	17 (9)	10 (5)
Chronic renal failure, n (%)[f]		
Stage I	60 (31)	55 (28)
Stage II	69 (35)	76 (39)
Stage III	51 (26)	41 (21)
Stage IV	15 (8)	21 (11)
Stage V	0 (0)	0 (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 which 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]	52 (27)	68 (36)
Study discontinuation, n (%)[j]	31 (16)	41 (22)

a. Number of randomized patients. Values which are based on different patient numbers are marked in the corresponding line, provided the deviation is relevant.
b. Summary: Native Americans or Alaskans, Native Hawaiians or Other Pacific Islanders, and mixed ancestry.
c. IQWiG calculations.
d. Based on immunofixation or measurement of free light chains.
e. Mayo stage based on the combination of the risk factors NT-proBNP (threshold > 332 ng/L) and hs-cTnT (threshold > 54ng/L). The protocol excluded patients in stage IIIb. All study participants were in stage IIIa at screening, but some had progressed to stage IIIb by Day 1 of Cycle 1.
f. Based on the estimated glomerular filtration rate eGFR.
g. Estimated cytogenetic risk is based on FISH or karyotyping; relative 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) oder t (4; 14), del17p (by karyotyping).
h. Of 155 patients (intervention arm) and 166 patients (comparator arm) with available cytogenetic risk assessment.
i: Treatment discontinuation before reaching of the maximum cycle number planned as per protocol. The most common reasons for treatment discontinuation were death (38% versus 21%), receipt of ASCT (23% versus 4%), AEs (15% versus 12%), receipt of subsequent therapy (10% versus 34%), and disease progression (MOD-PFS) (4% versus 16%).
j. Reasons for study discontinuation were: death (87% versus 66%), withdrawal of consent (13% versus 32%), and loss to follow-up (0% versus 2%).

Table 9: Characterization of the study population – RCT, direct comparison: Daratumumab + VCd vs. VCd (multipage table)

Study Characteristic Category	Daratumumab + VCd N[a] = 195	VCd N[a] = 193
ASCT: autologous stem cell transplantation; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; f: female; FISH: fluorescence-in-situ-hybridization; 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 (or included) patients; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; NYHA: New York Heart Association; RCT: randomized controlled trial; SD: standard deviation; VCd: bortezomib + cyclophosphamide + dexamethasone		

Patient characteristics are balanced between the two treatment groups of the ANDROMEDA study. Patients were slightly above 60 years on average and predominantly white (76%). At 45%, the percentage of women was slightly higher in the daratumumab + VCd arm than in the comparator arm, at 39%. A total of 9% of included patients had an ECOG-PS of 2. A total of 26% of patients had ≥ 3 organs affected by amyloidosis. The most commonly affected organs were the heart (71%) and kidney (59%). In total, 24% of patients included in the study resided in a country which typically does not offer stem cell transplantations for patients with AL amyloidosis.

Study discontinuation was less common in the daratumumab + VCd arm than in the comparator arm (16% versus 22%). By the data cut-off date, 27% in the intervention arm and 36% in the control arm had discontinued treatment before reaching the maximum number of cycles (24 and 6, respectively) defined by the protocol. In the intervention arm, 141 patients (72%) were still being treated with daratumumab on the data cut-off date. As defined in the study protocol, VCd treatment was already complete at 6 cycles at the present data cut-off (see section on data cut-offs).

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

Table 10: Information on the course of the study – RCT, direct comparison: Daratumumab + VCd vs. VCd

Study **Duration of the study phase** **Outcome category**	**Daratumumab + VCd**	**VCd**
ANDROMEDA		
Treatment duration [months]	N = 193	N = 188
Median [min; max][a]	9.6 [0.0; 21.2]	5.3 [0.0; 7.3]
Mean (SD)	9.7 (5.2)	4.4 (1.7)
Follow-up duration [months]	N = ND	N = ND
Overall survival		
Median[b] [min; max]	11.9 [ND]	11.1 [ND]
Mean (SD)	ND	ND
Morbidity (major organ deterioration[c])		
Median[b] [min; max]	11.1 [ND]	10.4 [ND]
Mean (SD)	ND	ND
Morbidity, health-related quality of life (EORTC QLQ-C30; EQ-5D VAS, SF-36)		
Median[d] [min; max]	ND	ND
Mean (SD)	ND	ND
Side effects		
Median[e] [min; max]	ND	ND
Mean (SD)	ND	ND

a. Median [min; max] treatment duration, expressed in cycles: 11 [1; 23] vs. 6 [1; 6]; by the data cut-off date, the maximum number of cycles (24 or 6) had been reached by none of the patients in the intervention arm and by 121 (64%) patients in the control arm. As defined in the study protocol, at the present data cut-off, VCd treatment was already complete at 6 cycles.
b. Inverse Kaplan-Meier method.
c. Data for the combined outcome of MOD-PFS.
d. The data provided by the company on median follow-up duration (9.2 months in the intervention arm and 6.1 months in the comparator arm) are based on the time to the last survey prior to subtherapy. It is unclear why the company disregarded planned surveys after the start of subsequent therapy in its calculation of follow-up durations.
e. The data provided by the company on median follow-up duration (10.6 months in the intervention arm and 6.3 months in the comparator arm) are based on the individual treatment duration + 30 days. Therefore, these data represent merely approximations, not the medians of the actual follow-up durations.

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; RCT: randomized controlled trial; SD: standard deviation; SF-36: Short Form-36 Health Survey; VAS: visual analogue scale; VCd: bortezomib + cyclophosphamide + dexamethasone

Due to the longer planned treatment duration of a maximum of 24 cycles in the intervention arm versus a maximum of 6 cycles in the comparator arm, the median and mean treatment durations in the intervention arm are longer than those in the comparator arm (median: 9.6 months versus 5.3 months; mean: 9.7 months versus 4.4 months). For the outcome of major

organ deterioration, the mean follow-up durations are roughly comparable between treatment groups. Since the follow-up duration for side effects outcomes is linked to treatment duration (see Table 8), the follow-up duration in the daratumumab + VCd arm is likewise longer than in the VCd arm. Unlike side effects, patient-reported morbidity and health-related quality of life outcomes continued to be surveyed even after the end of treatment (regarding between-arm differences in follow-up frequencies, see Section 2.4.2 on risk of bias).

The information provided by the company on median follow-up duration for the patient-reported outcomes (9.2 months in the intervention arm and 6.1 months in the comparator arm) are based on the time to the last survey prior to subsequent therapy. It is unclear why the company disregarded planned surveys after the start of subsequent therapy in its calculation of follow-up durations.

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

Table 11: Information on subsequent therapies[a] – RCT, direct comparison: Daratumumab + VCd vs. VCd

Study Drug class Drug	Patients with subsequent therapy n (%)	
	Daratumumab + VCd N = 193	VCd N = 188
ANDROMEDA		
≥ 1 anti-plasma cell therapy	20 (10.4)	90 (47.9)
Autologous stem cell transplantation	13 (6.7)	20 (10.6)
Antineoplastic agents	18 (9.3)	85 (45.2)
Alkylating agents	15 (7.8)	39 (20.7)
Melphalan	14 (7.3)	26 (13.8)
Cyclophosphamide	1 (0.5)	13 (6.9)
Other antineoplastic agents	3 (1.6)	64 (34.0)
Daratumumab	1 (0.5)	48 (25.5)
Bortezomib	1 (0.5)	26 (13.8)
Ixazomib	1 (0.5)	2 (1.1)
Carfilzomib	0 (0)	1 (0.5)
Isatuximab	0 (0)	1 (0.5)
Venetoclax	0 (0)	1 (0.5)
Corticosteroids for systemic use	4 (2.1)	53 (28.2)
Dexamethasone	4 (2.1)	53 (28.2)
Methylprednisolon	1 (0.5)	0 (0)
Prednison	0 (0)	1 (0.5)
Immunosuppressants	6 (3.1)	30 (16.0)
Lenalidomide	4 (2.1)	23 (12.2)
Pomalidomide	3 (1.6)	8 (4.3)

a. No data available on treatment regimens.

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

As per study protocol, patients were to not receive any subsequent therapies, if possible, before completion of the first 6 cycles, unless the MOD-PFS outcome was reached. Nevertheless, depending on haematological response and organ function, treatment discontinuation was possible starting in Cycle 4. For Cycle 7 and thereafter, the study protocol provided precise recommendations regarding subsequent therapy. Depending on the haematological response and organ function, it was possible to consider either (i) continuation of daratumumab monotherapy (in the intervention arm) and continued monitoring (in the comparator arm) until progression or (ii) a subsequent therapy, or the protocol recommended (iii) subsequent therapy. Continued follow-up in the control arm was unreservedly recommended only for patients who exhibited a response (i.e. partial response [PR] or better) in the first 6 cycles and additionally, improved organ function from baseline. In other cases, subsequent therapy was to be

considered; in the absence of a haematological response and simultaneously deteriorated organ function, the study protocol explicity recommended subsequent therapy. These specifications are largely in line with treatment recommendations [12,14,17].

There were no restrictions concerning subsequent therapies. Information on subsequent therapies is provided only regarding the drug, not the treatment regimen.

In the intervention arm, the drug most commonly used for subsequent therapy was melphalan (7.3%). In the comparator arm, the drugs dexamethasone (28.2%) and daratumumab (25.5%) were most commonly used. ASCT as subsequent therapy was received by 6.7% of patients in the intervention arm and 10.6% of patients in the comparator arm. It must be noted that the study protocol excluded from participation any patients with ASCT planned to be performed within the first 6 cycles of treatment with the study drug.

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 vs. VCd

Study	Adequate random sequence generation	Allocation concealment	Blinding		Results-independent reporting	Lack of other aspects	Risk of bias at study level
			Patients	Treatment providers			
ANDROMEDA	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial; VCd: bortezomib + cyclophosphamide + dexamethasone							

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

Restrictions resulting from the open-label study design are described in Section 2.4.2 under risk of bias at outcome level.

Transferability of the study results to the German healthcare context

The company explains that, due to the rarity of the disease, the ANDROMEDA study is conducted in as many as 22 countries. It lists the ancestries of study participants with relative frequencies and concludes that there is no evidence of ancestries being associated with relevant effect differences. Moreover, the company asserts that likewise, no evidence of effect difference was found for the stratification attribute of "countries which typically offer stem cell transplantation for patients with AL amyloidosis (list A: yes / list B: no)". Finally, the company argues that in the ANDROMEDA study, there was no evidence of any biodynamic or kinetic

differences which would meaningfully impact study results between Germany and other specific population groups or countries. Hence, the company posits that the results are generally transferable to the German healthcare context, in consideration of the uncertainty associated with the transferability of clinical data.

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

2.4 Results on added benefit

2.4.1 Outcomes included

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

- Mortality
  - Overall survival
- Morbidity
  - Major organ deterioration
  - Symptoms, measured with the EORTC QLQ-C30
  - Health status, surveyed using the EQ-5D VAS
- Health-related quality of life
  - Surveyed with the EORTC QLQ-C30
  - Surveyed with the SF-36
- Side effects
  - SAEs
  - Severe AEs (CTCAE grade ≥ 3)
  - Discontinuation due to AEs
  - Peripheral neuropathies (HLT, AEs)
  - Further specific AEs, if any

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

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

Table 13: Matrix of outcomes – RCT, direct comparison: Daratumumab + VCd vs. VCd

Study	Outcomes										
	Overall survival	Major organ deterioration[a]	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30 and SF-36)	SAEs	Severe AEs[b]	Discontinuation due to AEs[c]	Peripheral neuropathy (HLT, AEs)	Skin and subcutaneous tissue disorders (SOC[d], AEs)	Hypokalemia (PT[d], severe AEs[b])
ANDROMEDA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[e]	Yes	Yes

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

b. Operationalized as CTCAE grade ≥ 3.
c. Discontinuation of ≥ 1 drug component.
d. Coded using MedDRA.
e. Of interest are patient-relevant, symptomatic peripheral neuropathy CTCAE grade ≥ 2. However, there were no data on the percentage of patients with CTCAE grade 1.

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 Regulatory Activities; PT: preferred term; 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

The company's dossier presents results for the composite outcome of major organ deterioration. The outcome is operationalized as time to occurrence of any one of the following events:

- Clinical manifestation of cardiac failure, defined as need for cardiac transplant, left ventricular assist device, or intra-aortic balloon pump
- Clinical manifestation of renal failure, defined as the development of end-stage renal disease (need for haemodialysis or renal transplant)

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

- Proceeding from CHR: abnormal free light-chain ratio (doubling of light chains and light chains > upper limit of normal range)

- Proceeding from CHR, very good partial response (VGPR) or PR: 50% increase in serum M protein to > 0.5 g/dL or 50% increase in urine M protein to > 200 mg/day
- Increase in involved free light chains by > 50% to >100 mg/L

In the present benefit assessment, the components major organ deterioration and death (overall survival) were analysed as independent patient-relevant outcomes. The composite outcome of MOD-PFS itself was excluded from the benefit assessment because the component of haematologic progression of disease is an outcome based solely on laboratory parameters.

EQ-5D VAS, EORTC QLQ-C30, and SF-36

For EORTC QLQ-C30, the company's dossier presented responder analyses of time to reach a change by ≥ 10 points and by ≥ 15% of the scale range (scale ranges of 0–100). As discussed in the IQWiG General Methods [1,20], a response criterion should be predefined to cover at least 15% of the range of an instrument's scale (for post hoc analyses, exactly 15% of the range of the scale) in order to reflect with sufficient certainty a change which is perceivable for patients. For EORTC QLQ-C30 and its supplementary modules, the analysis with the previously accepted response threshold of 10 points was viewed as a sufficient approximation to an analysis with a 15% threshold (15 points) and was used for the benefit assessment (for an explanation, see dossier assessment A20-97 [21]). Irrespective of the above, for a transition period until the revised module templates for the dossier enter into force, primarily analyses with the previously accepted response threshold of 10 points are used for the EORTC QLQ-C30 and all additional EORTC modules (see FAQs from the G-BA: [22]).

For the outcome of health status (EQ-5D VAS), the company's dossier presents responder analyses for time to deterioration by ≥ 7 points or ≥ 10 points, respectively (scale range 0 – 100). These were not used for the dossier assessment but presented as supplementary information in Appendix D of the full dossier assessment. Further, the company presented responder analyses with the response criterion of 15% of the scale range. They were used for deriving added benefit.

On health-related quality of life, the company submitted results surveyed with the EORTC QLQ-C30 as well as results surveyed with SF-36. For the PCS and MCS, the company presented responder analyses of time to deterioration by ≥ 5 points. These were not used for the dossier assessment but presented as supplementary information in Appendix D of the full dossier assessment. Further, the company presented responder analyses with the response criterion of 15% of the scale range. For this purpose, the company determined the scale range based on the empirical minimum and maximum values of the PCS and MCS, using published values from the 1998 standard sample in the SF-36v2 manual, version 2 from 2007. It calculated a response criterion of 10.05 for PCS and 10.80 for MCS. Using the empirical minima and maxima of the 2009 standard sample (published in the current version 3 of the manual from 2011 [23]) and a response criterion of 15%, slightly below 10 points result for the two summary scores (PCS: 9.4; MCS: 9.6; for a detailed explanation, see [24]). In the present situation, the

response criteria calculated by the company for the PCS and MCS can be used because, firstly, they are close to the response criteria determined using the current manual. Secondly, due to the results which are numerically in favour of the intervention but not statistically significant (see Table 15), reporting bias can be ruled out.

For the symptoms and health-related quality of life outcomes, which were surveyed using EORTC QLQ-C30, EQ-5D VAS, and SF-36, the company presented responder analyses for time to deterioration and time to improvement. Time to deterioration has been used. Due to the course of disease to be expected in the present therapeutic indication and taking into account the distribution of absolute values of the scales at baseline, an analysis on the deterioration of health status is of primary relevance for the present benefit assessment.

Since the company does not provide any detailed information on the operationalization of deterioration, it is assumed to be the time to 1st deterioration.

According to the statistical analysis plan, time to deterioration was prespecified through distribution-based methods. Death due to progression was also defined as deterioration. In the operationalization found in Module 4 A of deterioration by ≥ 10 points, however, there is nothing to suggest that death was defined as deterioration.

For the comparator arm, the company presented information on return rates for patient-reported outcomes only up to Cycle 6 (planned treatment end). According to the prespecified follow-up observation, however, surveys took place after treatment end. This was also confirmed when analysing the Kaplan-Meier curves on patient-reported outcomes (see Appendix C of the full dossier assessment). Overall, complete return rates for both study arms across the entire course of the study are therefore missing.

Individual items of the EORTC QLQ Ovarian Cancer 28 (OV28), Multiple Myeloma 20 (MY20) and Prostate Cancer 25 (PR25)

Beyond results on EORTC QLQ-C30, the company's dossier presents results on the individual items: tingling hands and feet from EORTC QLQ-MY20, bloated feeling in abdomen/stomach from EORTC QLQ-OV28, and swelling in legs or ankles from EORTC QLQ-PR25. The study protocol justifies the use of these items using the Lin 2015 study on symptoms in AL amyloidosis [25]. The selection of the analysed individual items does not follow directly from the Lin 2015 results since the study identified a total of 25 symptoms of AL amyloidosis, including 11 common symptoms. The company did not justify the selection of the 3 symtpoms. Furthermore, EORTC stipulates the use of individual items in the form of an itemized list only in connection with EORTC QLQ-C30 and a validated additional module [26]. Therefore, the individual items have been disregarded in the present assessment. Irrespective of this, neither the presented analyses of deterioration nor those of improvement show any advantages or disadvantages of daratumumab + VCd which are statistically significant and more than minor.

Side effects

As per study protocol, progression events of systemic AL amyloidosis were not surveyed as AEs. No information is available on the definition of progression events not surveyed.

Discontinuation due to AEs

For the outcome of discontinuation due to AEs, the company's Module 4 A presented analyses on discontinuation of all drug components as well as of ≥ 1 drug component. The analysis on the discontinuation of ≥ 1 drug component was used since any AE which leads to a discontinuation of any drug component is relevant.

Peripheral neuropathy (HLT, AEs)

In the ANDROMEDA study, 97 of 105 patients (92%) who developed peripheral neuropathy (HLT) over the course of the study exhibited peripheral sensory neuropathy (PT). Neuropathies of interest are patient-relevant, symptomatic peripheral neuropathies, i.e. neuropathy of CTCAE grade ≥ 2. However, information on this topic or on patients with grade 1 peripheral neuropathy is not available. Therefore, no usable data are available for the outcome of peripheral neuropathy (HLT, AEs). Independently of this, the analysis presented by the company shows no statistically significant differences between treatment groups. Severe AEs (CTCAE grade ≥ 3) are not additionally analysed since they make up only 10% of all peripheral neuropathies.

2.4.2 Risk of bias

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

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

Study	Study level	Outcomes										
		Overall survival	Major organ deterioration[a]	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30 and SF-36)	SAEs	Severe AEs[b]	Discontinuation due to AEs[c)]	Peripheral neuropathy (HLT, AEs)	Skin and subcutaneous tissue disorders (SOC, AEs)	Hypokalaemia (PT, severe AEs[b)])
ANDROMEDA	L	L	H[d]	H[e, f]	H[e, f]	H[e, f]	H[d]	H[d]	H[e]	-[g]	H[d, e]	H[d]

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

b. Operationalized as CTCAE grade ≥ 3.
c. Discontinuation of ≥ 1 drug component.
d. Incomplete observations for potentially informative reasons.
e. Absence of blinding with subjective recording of outcomes or subjective decision on discontinuation.
f. Difference in survey intervals between treatment arms.
g: Neuropathies of interest are patient-relevant, symptomatic peripheral neuropathies of CTCAE grade ≥ 2. However, there is no information on the percentage of patients with CTCAE grade 1; also see Section 2.4.1.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; H: high; HLT: high-level term; L: low; PT: preferred term; 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 of overall survival, the risk of bias of results of all other outcomes is rated as high. Hence, the assessment departs from that by the company in the outcomes of major organ deterioration and severe AEs, for which the company rates the risk of bias as low. For each of them, the rating of high risk of bias is justified below.

For the outcome of major organ deterioration, the risk of bias is rated as high. The outcome is a component of the composite outcome of MOD-PFS, defined as the occurrence of major organ deterioration, haematologic progression of disease, or death. For the outcome of MOD-PFS, follow-up is prespecified until the occurrence of the 1st event regarding one of the 3 components. As a result, the follow-up period for the component of major organ deterioration discontinues early if haematologic progression of disease has occurred previously. For this reason, observations are incomplete for potentially informative reasons.

The risk of bias for each of the results on health status (EQ-5D VAS) as well as the outcomes of symptoms (EORTC QLQ-C30), and health-related quality of life (EORTC QLQ-C30 functioning scales on global health status, SF-36) is rated as high. This is due to absence of blinding in subjective recording of outcomes. Another aspect is the between-arm difference in survey intervals which developed over the course of the study regarding patient-reported outcomes. The rationale is provided below.

Surveys on patient-reported outcomes were predefined as follows:

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

The planned treatment duration is 24 cycles in the intervention arm and 6 cycles in the comparator arm. In both study arms, surveys were conducted on Day 1 of each of the first 6 cycles, unless the medication was discontinued early. Due to differences in planned treatment duration as per study protocol, the intervals between survey time points are larger in the comparator arm versus the control arm at the latest from Cycle 8: from Cycle 7, surveys are conducted every 8 weeks in the intervention arm versus, in the comparator arm, initially 30 days after the last medication (corresponds to the start of Cycle 7 unless the medication was discontinued early) and then only every 6 months until disease progression. This means that a deterioration, which is used as the operationalization in the present benefit assessment, might be noticed much later in the comparator arm than in the intervention arm or might even be overlooked.

The results on each of the outcomes of the side effects category are rated as highly biased.

The analyses of the outcomes in the side effects category include all events which occurred within 30 days after the last administration of the study drug or until the start of a subsequent anti-plasma cell therapy. In light of differences in planned treatment duration (24 cycles versus 6 cycles), at a 28-day cycle duration in the comparator arm, events are included only up to about 7 months after study start. A comparison of the two treatment arms is therefore possible only for this first 7-month period because after that, all times for the patients still under risk in the comparator arm are censored. Events occurring after this time period in the intervention arm are therefore not included in the estimate of hazard ratio (HR).

In the present situation, incomplete observations for potentially informative reasons are therefore of importance only for approximately the first 7 months after study start. Hence, the

assessment checked whether censoring which occurred within this time period and hence resulted from early treatment discontinuation was for potentially informative reasons.

A total of 68 patients in the comparator arm (36%) discontinued treatment early, within the first 6 months. In the intervention arm, 34 patients (18%) already discontinued before Cycle 7. Some of the reasons for discontinuation might have been potentially informative (receipt of subsequent therapy, including ASCT, disease progression [MOD-PFS], AEs). Hence, for outcomes in the side effects category other than the outcome of discontinuation due to AEs, the risk of bias is rated as high due to incomplete observation for potentially informative reasons.

For the outcome of discontinuation due to AEs, absence of blinding is the sole reason for the high risk of bias.

For the specific AE of skin and subcutaneous tissue disorders (SOC, AEs), absence of blinding – alongside incomplete observation for potentially informative reasons – is rated as an additional biasing aspect.

2.4.3 Results

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

Common AEs, common SAEs, common severe AEs (CTCAE grade ≥ 3), and discontinuation due to AEs are presented in Appendix B of the full dossier assessment. Kaplan-Meier curves on the outcomes included in the benefit assessment are found in Appendix C of the full dossier assessment.

Table 15: Results (mortality, morbidity, health-related quality of life, AEs) – RCT, direct comparison: daratumumab + VCd vs. 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]; p-value[a]
ANDROMEDA					
Mortality					
Overall survival	195	NR 27 (13.8)	193	NA 29 (15.0)	0.90 [0.53; 1.53]; 0.706
Morbidity					
Major organ deterioration	195	NA 1 (0.5)	193	NA 7 (3.6)	0.12 [0.01; 1.01]; 0.020
Clinical manifestation of cardiac failure, defined as need for cardiac transplant, left ventricular assist device, or inta-aortic balloon pump	No data available				
Clinical manifestation of renal failure, defined as the development of end-stage renal disease (need for haemodialysis or renal transplant)	No data available				
Symptoms EORTC QLQ-C30, time to deterioration[b, c]					
Fatigue	195	2.1 [1.9; 3.7] 116 (59.5)	193	1.9 [1.9; 2.8] 132 (68.4)	0.78 [0.60; 1.00]; 0.054
Nausea and vomiting	195	NR [7.8; NC] 70 (35.9)	193	8.2 [4.7; NC] 80 (41.5)	0.75 [0.54; 1.03]; 0.076
Pain	195	4.1 [2.8; 6.5] 107 (54.9)	193	3.8 [2.9; 4.8] 103 (53.4)	1.01 [0.77; 1.34]; 0.926
Dyspnoea	195	21.3 [9.7; 21.3] 71 (36.4)	193	3.8 [2.8; 5.7] 99 (51.3)	0.62 [0.45; 0.84]; 0.002
Insomnia	195	4.6 [2.9; 17.6] 94 (48.2)	193	3.8 [2.9; 6.5] 94 (48.7)	1.01 [0.76; 1.35]; 0.934
Appetite loss	195	6.5 [4.1; NC] 86 (44.1)	193	5.0 [3.7; 6.5] 96 (49.7)	0.87 [0.65; 1.17]; 0.348
Constipation	195	12.3 [3.9; NC] 85 (43.6)	193	4.9 [3.3; 14.9] 88 (45.6)	0.91 [0.67; 1.23]; 0.527
Diarrhoea	195	7.5 [4.7; NC] 86 (44.1)	193	6.2 [3.8; 12.2] 88 (45.6)	0.89 [0.66; 1.21]; 0.454
Health status (EQ-5D VAS, time to deterioration[c,d])	195	13.0 [4.7; NC] 78 (40.0)	193	4.9 [3.7; 15.4] 87 (45.1)	0.88 [0.65; 1.20]; 0.418

Table 15: Results (mortality, morbidity, health-related quality of life, AEs) – RCT, direct comparison: daratumumab + VCd vs. 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]; p-value[a]
Health-related quality of life					
EORTC QLQ-C30, time to deterioration[c, e]					
Global health status	195	4.7 [2.8; 7.4] 102 (52.3)	193	2.9 [2.2; 3.8] 112 (58.0)	0.86 [0.66; 1.14]; 0.295
Physical functioning	195	4.7 [2.8; 12.3] 94 (48.2)	193	3.8 [2.8; 4.7] 106 (54.9)	0.81 [0.61; 1.08]; 0.153
Role functioning	195	2.3 [1.9; 4.6] 111 (56.9)	193	2.8 [2.0; 3.7] 121 (62.7)	0.90 [0.69; 1.17]; 0.445
Emotional functioning	195	17.6 [17.6; NC] 64 (32.8)	193	5.0 [4.0; NC] 82 (42.5)	0.69 [0.50; 0.97]; 0.032
Cognitive functioning	195	5.6 [3.9; 7.9] 99 (50.8)	193	3.8 [2.8; 4.7] 110 (57.0)	0.78 [0.59; 1.03]; 0.085
Social functioning	195	2.8 [1.9; 3.1] 111 (56.9)	193	2.9 [2.0; 3.8] 115 (59.6)	1.01 [0.78; 1.32]; 0.931
SF-36, time to deterioration[c, f]					
Physical Component Summary (PCS)	195	19.3 [19.3; NC] 58 (29.7)	193	12.5 [8.5; NC] 71 (36.8)	0.76 [0.53; 1.07]; 0.117
Mental Component Summary (MCS)	195	14.9 [9.3; NC] 68 (34.9)	193	NR [6.2; NC] 69 (35.8)	0.93 [0.67; 1.31]; 0.688
Vitality Social functioning Emotional role Mental health Physical functioning Physical role Physical pain General health perception	No data available				

Table 15: Results (mortality, morbidity, health-related quality of life, AEs) – RCT, direct comparison: daratumumab + VCd vs. 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]; p-value[a]
Adverse events[g]					
AEs (supplementary information)	193	0.1 [0.1; 0.1] 189 (97.9)	188	0.2 [0.1; 0.3] 185 (98.4)	–
SAEs	193	NR [12.0; NC] 83 (43.0)	188	NA 68 (36.2)	1.01 [0.73; 1.41]; 0.943
Severe AEs[h]	193	3.6 [2.4; 4.9] 119 (61.7)	188	3.5 [2.5; 4.4] 114 (60.6)	1.01 [0.78; 1.32]; 0.909
Discontinuation due to AEs (≥ 1 drug component)	193	NA 20 (10.4)	188	NR 17 (9.0)	1.04 [0.54; 2.01]; 0.895
Peripheral neuropathy (HLT, AEs)	No usable data[i]				
Skin and subcutaneous tissue disorders (SOC, AEs)	193	14.9 [6.6; NC] 86 (44.6)	188	NC 42 (22.3)	1.99 [1.37; 2.91]; < 0.001
Hypokalaemia (PT, severe AEs[h])	193	NR 3 (1.6)	188	NR 10 (5.3)	0.27 [0.07; 0.997]; 0.0495

a. HR and CI: Cox proportional hazards model; stratified by cardiac stage at study start (Mayo stage I / Mayo stage II / Mayo stage IIIa), countries which typically offer stem cell transplantation for patients with AL amyloidosis (list A: yes / list B: no) and renal function status at baseline (CrCl < 60 mL/min / CrCl ≥ 60 mL/min); p-value: for the outcomes of overall survival and major organ deterioration, stratified log rank test; for all other outcomes, p-value from the above-described Cox proportional hazards model.
b. Clinically relevant deterioration is defined as an increase by ≥ 10 points from baseline on a scale of 0 to 100 points.
c. Presumably time to 1st deterioration.
d. Clinically relevant deterioration is defined as decrease by ≥ 15 points from baseline on a scale of 0 to 100 points.
e. Clinically relevant deterioration is defined as a decrease by ≥ 10 points from baseline on a scale of 0 to 100 points.
f. Clinically relevant deterioration is defined as decrease by ≥ 10.80 points (MCS) or by ≥ 10.05 points (PCS) from baseline.
g. In the interpretation of results on side effects, it must be noted that the much shorter planned treatment duration and the associated discontinuation of follow-up observation in the comparator arm lead to the hazard ratio reflecting a comparison over only the first 7 months after randomization.
h. Operationalized as CTCAE grade ≥ 3.
i. Neuropathies of interest are patient-relevant, symptomatic peripheral neuropathies of CTCAE grade ≥ 2. However, no information is available on the percentage of patients with CTCAE grade 1; see Section 2.4.1).

AE: adverse event; 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; MCS: Mental Component Summary; MY20: Multiple Myeloma Module 20; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; NR: not reached; OV28: Ovarian Cancer Module 28; PCS: Physical Component Summary; PR25: Prostate Cancer Module 25; PT: preferred term; 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

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes (see Section 2.3.2).

Mortality

Overall survival

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

This concurs with the company's assessment.

Morbidity

Major organ deterioration

The outcome of major organ deterioration is a component of the composite outcome of MOD-PFS. The result of the stratified log-rank test was used for deriving added benefit since its use was planned for the composite outcome of MOD-PFS.

For the outcome of major organ deterioration, a statistically significant difference was found in favour of daratumumab + VCd. This results in a hint of added benefit of daratumumab + VCd in comparison with VCd.

The assessment departs from that submitted by the company. The company derived an indication of added benefit across outcomes for the morbidity category.

Symptoms

Symptoms outcomes were surveyed using the EORTC QLQ-C30 instrument. Time to deterioration by ≥ 10 points was used.

Dyspnoea

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

To assess added benefit, the company used the results on both deterioration and improvement. For both operationalizations, statistically significant differences in favour of daratumumab + VCd were found.

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

No statistically significant difference between treatment arms was found for any of the outcomes of fatigue, nausea and vomiting, pain, insomnia, appetite loss, constipation, or diarrhoea. Consequently, there was no hint of added benefit of daratumumab + VCd in comparison with VCd for any of them; an added benefit is therefore not proven.

The assessment of the above outcomes concurs with the assessment by the company in that the company did not report any statistically significant differences in terms of deterioration or improvement.

The conclusions on added benefit for symptoms outcomes depart from those by the company, which derived an indication of added benefit for the entire morbidity outcome category.

Health status

Health status was surveyed by EQ-5D. Time to deterioration by ≥ 15 points was used.

For the outcome of health status, no statistically significant difference between treatment groups was found. There was therefore no hint of added benefit of daratumumab + VCd in comparison with VCd; an added benefit is therefore not proven.

For assessing added benefit, the company used the results on deterioration as well as on improvement of health status by ≥ 15 points, but a statistically significant difference was found only for improvement in favour of daratumumab + VCd.

The conclusion on added benefit for the outcome of health status (EQ-5D VAS) departs from that drawn by the company, which derived an indication of added benefit for the entire outcome category of morbidity.

Health-related quality of life

EORTC QLQ-C30

Health-related quality of life outcomes were surveyed using the EORTC QLQ-C30 instrument. Time to deterioration by ≥ 10 points was used.

Emotional functioning

For the outcome of emotional functioning, a statistically significant difference was found in favour of daratumumab + VCd. This results in a hint of added benefit of daratumumab + VCd in comparison with VCd.

For assessing added benefit, the company used the results on deterioration as well as improvement, but a statistically significant difference was found only for deterioration, in favour of daratumumab + VCd.

Physical functioning, role functioning, cognitive functioning, social functioning, global health status

No statistically significant difference between treatment groups was found for any of the outcomes of physical functioning, role functioning, cognitive functioning, social functioning, and global health status. Consequently, there was no hint of added benefit of daratumumab + VCd in comparison with VCd for any of them; an added benefit is therefore not proven.

To assess added benefit, the company used the results on both deterioration and improvement. No statistically significant difference between treatment arms was found for any of the outcomes of physical functioning, role functioning, or social functioning. With regard to improvement of global health status, the company reported a statistically significant advantage of daratumumab + VCd in comparison with VCd.

Overall, considering both improvement and deterioration, the company derived a hint of added benefit for the outcome category of health-related quality of life.

SF-36

For health-related quality of life, surveyed using SF-36, the analyses of time to deterioration used a threshold of ≥ 10.80 points for MCS and ≥ 10.05 points for PCS.

No statistically significant difference between treatment groups was found for either PCS or MCS. Consequently, there was no hint of added benefit of daratumumab + VCd in comparison with VCd for any of them; an added benefit is therefore not proven.

No results were available on the 8 subscales of the SF-36.

This conclusion concurs with that drawn by the company in that the company did not report any statistically significant differences for the analysis of PCS or MCS improvement or deterioration. The company derived a hint of added benefit across outcomes for the health-related quality of life category.

Side effects

Regarding the interpretation of side effects results, it must be noted that due to the much shorter planned treatment duration and the associated discontinuation of follow-up in the comparator arm, the hazard ratio reflects a comparison across only the first 7 months after randomization.

SAEs, severe AEs (CTCAE grade ≥ 3)

For the outcomes of SAEs and severe AEs (CTCAE ≥ grade 3), no statistically significant difference between treatment groups was found. Consequently, no hint of greater or lesser harm from daratumumab + VCd versus VCd can be derived for any of them; greater or lesser harm is therefore not proven.

The conclusions on the outcomes of SAEs and severe AEs (CTCAE grade ≥ 3) are in line with those drawn by the company in that the company did not report any statistically significant differences between treatment groups for any of the outcomes.

Discontinuation due to AEs (discontinuation of ≥ 1 drug component)

For the outcome of discontinuation due to AEs (≥ 1 drug component), no statistically significant difference between treatment groups was found. Consequently, no hint of greater or lesser harm

from daratumumab + VCd in comparison with VCd can be derived for any of them; greater or lesser harm is therefore not proven.

The assessment on the outcome of discontinuation due to AEs is in line with the conclusion drawn by the company in that the company did not report any statistically significant differences between treatment groups for the outcome of discontinuation due to AEs (discontinuation of ≥ 1 drug component), nor for discontinuation of all drug components due to AEs.

Peripheral neuropathy (HLT, AEs)

No usable data were available on the outcome of peripheral neuropathy (HLT, AEs) (see Section 2.4.1). Consequently, no hint of greater or lesser harm from daratumumab + VCd versus VCd can be derived for any of them; greater or lesser harm is therefore not proven.

For the outcome of peripheral neuropathy (HLT, AEs), the company did not report any statistically significant differences between treatment groups.

Skin and subcutaneous tissue disorders (SOC, AEs)

For the outcome of skin and subcutaneous tissue disorders (SOC, AEs), a statistically significant difference was found to the disadvantage of daratumumab + VCd. This results in a hint of greater benefit of daratumumab + VCd in comparison with VCd.

The conclusion on the statistically significant difference to the disadvantage of daratumumab + VCd is in line with that drawn by the company.

Hypokalaemia (PT, severe AEs)

For the outcome of hypokalaemia (PT, severe AEs), a statistically significant difference was found in favour of daratumumab + VCd. This results in a hint of lesser harm of daratumumab + VCd in comparison with VCd.

The conclusion on the statistically significant difference in favour of daratumumab + VCd is in line with that drawn by the company.

The prior assessment of results for all outcomes of the side effects outcome category departs from the conclusions drawn by the company in that the company neither conducted any outcome-specific derivation of added benefit nor derived any proof of added benefit or harm for the side effects outcome category.

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics are relevant for the present assessment:

- Sex (female versus male)
- Age (< 65 versus ≥ 65 years)
- Cardiac involvement (yes versus no)

In the present situation, however, the results from the subgroup analyses are deemed uninterpretable and were disregarded. The reasoning is provided below.

The analysed subgroup characteristics are factors which are of importance in the choice of therapy and hence in the implementation of the ACT, individualized therapy, taking into account general health, comorbidity, and organ deterioration. The respective subgroups, e.g. older patients or patients with cardiac involvement, are associated with uncertainty regarding the implementation of the ACT, in addition to the uncertainty described above (see Section 2.3.2). Some patients in the ≥ 65-years subgroup might be better suited for a dual combination, for instance; or lenalidomide might be the more suitable individualized therapy in some patients in the no-cardiac-involvement subgroup. Consequently, only the total population of the ANDROMEDA study has been investigated in the present situation.

2.5 Probability and extent of added benefit

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

The approach for deriving an overall conclusion on any added benefit by aggregating the conclusions reached at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of added benefit at outcome level

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

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

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

Symptoms

Dyspnoea (EORTC QLQ-C30)

For the outcome of dyspnoea, no information which would lead to a severe/serious rating is available. Therefore, this outcome is allocated to the outcome category of non-serious/non-severe symptoms / late complications. The company did not allocate it to any outcome category.

Specific AEs

Skin and subcutaneous tissue disorders (SOC, AEs)

Only 4 patients with an event in the SOC skin and subcutaneous tissue disorders had a CTCAE severity of 3 or 4, and only 1 patient had a corresponding SAE. Therefore, the outcome is allocated to the outcome category of non-serious/non-severe AEs. This concurs with the company's assessment.

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

Outcome category **Outcome**	**Daratumumab + VCd vs. VCd** **Median time to event (months)** **HR [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
Overall survival	NR vs. NR 0.90 [0.53; 1.53]; p = 0.706	Lesser/added benefit not proven
Morbidity		
Major organ deterioration	NR vs. NR 0.12 [0.01; 1.01]; p = 0.020 Probability: hint	Outcome category: serious/severe symptoms / late complications Added benefit[c]; extent: minor[d]
Clinical manifestation of cardiac failure, defined as need for cardiac transplant, left ventricular assist device, or inta-aortic balloon pump	No data available	
Clinical manifestation of renal failure, defined as the development of end-stage renal disease (need for haemodialysis or renal transplant)	No data available	
Symptoms, EORTC QLQ-C30, deterioration by ≥ 10 points		
Fatigue	2.1 vs. 1.9 0.78 [0.60; 1.00]; p = 0.054	Lesser/added benefit not proven
Nausea and vomiting	NR vs. 8.2 0.75 [0.54; 1.03]; p = 0.076	Lesser/added benefit not proven
Pain	4.1 vs. 3.8 1.01 [0.77; 1.34]; p = 0.926	Lesser/added benefit not proven
Dyspnoea	21.3 vs. 3.8 0.62 [0.45; 0.84]; p = 0.002 Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $0.80 \leq CI_u < 0.90$ Added benefit; extent: minor
Insomnia	4.6 vs. 3.8 1.01 [0.76; 1.35]; p = 0.934	Lesser/added benefit not proven
Appetite loss	6.5 vs. 5.0 0.87 [0.65; 1.17]; p = 0.348	Lesser/added benefit not proven
Constipation	12.3 vs. 4.9 0.91 [0.67; 1.23]; p = 0.527	Lesser/added benefit not proven
Diarrhoea	7.5 vs. 6.2 0.89 [0.66; 1.21]; p = 0.454	Lesser/added benefit not proven
Health status		
EQ-5D VAS, deterioration by ≥ 15 points	13.0 vs. 4.9 0.88 [0.65; 1.20]; p = 0.418	Lesser/added benefit not proven

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

Outcome category **Outcome**	**Daratumumab + VCd vs. VCd** **Median time to event (months)** **HR [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Health-related quality of life		
EORTC QLQ-C30, deterioration by ≥ 10 points		
Global health status	4.7 vs. 2.9 0.86 [0.66; 1.14]; p = 0.295	Lesser/added benefit not proven
Physical functioning	4.7 vs. 3.8 0.81 [0.61; 1.08]; p = 0.153	Lesser/added benefit not proven
Role functioning	2.3 vs. 2.8 0.90 [0.69; 1.17]; p = 0.445	Lesser/added benefit not proven
Emotional functioning	17.6 vs. 5.0 0.69 [0.50; 0.97]; p = 0.032 Probability: hint	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Added benefit; extent: minor
Cognitive functioning	5.6 vs. 3.8 0.78 [0.59; 1.03]; p = 0.085	Lesser/added benefit not proven
Social functioning	2.8 vs. 2.9 1.01 [0.78; 1.32]; p = 0.931	Lesser/added benefit not proven
SF-36, deterioration		
Physical Component Summary (PCS), deterioration by ≥ 10.05 points	19.3 vs. 12.5 0.76 [0.53; 1.07]; p = 0.117	Lesser/added benefit not proven
Mental Component Summary (MCS), deterioration by ≥ 10.80 points	14.9 vs. NR 0.93 [0.67; 1.31]; p = 0.688	Lesser/added benefit not proven
Side effects[e]		
SAEs	NR vs. NR 1.01 [0.73; 1.41]; p = 0.943	Lesser/added benefit not proven
Severe AEs[f]	3.6 vs. 3.5 1.01 [0.78; 1.32]; p = 0.909	Lesser/added benefit not proven
Discontinuation due to AEs (≥ 1 drug component)	NR vs. NR 1.04 [0.54; 2.01]; p = 0.895	Lesser/added benefit not proven
Peripheral neuropathy (AEs)	No usable data[g]	Lesser/added benefit not proven
Diseases of the skin and subcutaneous tissue (AEs)	14.9 vs. NR 1.99 [1.37; 2.91]; p < 0.001 0.50 [0.34; 0.73][h] Probability: hint	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm; extent: considerable
Hypokalaemia (severe AEs[f])	NR vs. NR 0.27 [0.07; 0.997]; p = 0.0495 Probability: hint	Outcome category: serious/severe AEs $0.90 \leq CI_u < 1.00$ Lesser harm; extent: minor

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

Outcome category **Outcome**	**Daratumumab + VCd vs. VCd** **Median time to event (months)** **HR [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
a. Probability is stated whenever a statistically significant and relevant effect is present. b. Estimations of effect size are made depending on the outcome category, with different limits according to the upper limit of the confidence interval (CI_u). c. The result of the statistical test is determinative for deriving added benefit. d. Discrepancy between CI and p-value: extent rated as low. e. In the interpretation of results on side effects, it must be noted that the much shorter planned treatment duration and the associated discontinuation of follow-up observation in the comparator arm lead to the hazard ratio reflecting a comparison over only the first 7 months after randomization. f. Operationalized as CTCAE grade ≥ 3. g. Of interest is patient-relevant, symptomatic peripheral neuropathy CTCAE grade ≥ 2. However, there were no data on the percentage of patients with CTCAE grade 1. h. IQWiG calculation; reversed direction of effect to enable use of limits to derive the extent of added benefit. AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; MCS: Mental Component Summary; n: number of patients with (at least 1) event; N: number of analysed patients; NR: not reached; PCS: Physical Component Summary; QLQ-C30: Quality of Life Questionnaire – Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form-36 Health Survey; VAS: visual analogue scale VCd: bortezomib + cyclophosphamide + dexamethasone		

2.5.2 Overall conclusion on added benefit

Table 17 summarizes the results which were factored into the overall conclusion on the extent of added benefit.

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

Favourable effects	Unfavourable effects
Serious/severe symptoms / late complications ▪ Major organ deterioration: Hint of added benefit – extent: minor	
Non-serious/non-severe symptoms / late complications ▪ Dyspnoea: Hint of added benefit – extent: minor	-
Health-related quality of life ▪ Emotional functioning: Hint of added benefit – extent: minor	-
Serious/severe side effects[a] ▪ Hypokalaemia (severe AEs): hint of lesser harm – extent: minor	-
-	Non-serious/non-severe side effects[a] ▪ Diseases of the skin and subcutaneous tissue (AEs): hint of greater harm – extent: considerable

a. In the interpretation of results on side effects, it must be noted that the much shorter planned treatment duration and the associated discontinuation of follow-up observation in the comparator arm lead to the hazard ratio reflecting a comparison over only the first 7 months after randomization.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; VCd: bortezomib + cyclophosphamide + dexamethasone

On the basis of the ANDROMEDA study, conclusions can be drawn in this benefit assessment only on patients for whom VCd is the ACT individually best suited. No data are available on patients for whom treatment other than VCd is the best suited ACT. Therefore, added benefit is derived separately for these two patient groups.

Patients for whom VCd is the best suited ACT

Overall, several favourable effects in the outcome categories of serious/severe symptoms / late complications, non-serious/non-severe symptoms / late complications, health-related quality of life, and serious/severe side effects are counteracted by one unfavourable effect in the outcome category of non-serious/non-severe side effects. The favourable effects are of minor extent. The unfavourable effect of considerable extent in the outcome category of non-serious/non-severe side effects does not call the favourable effects into question. In summary, for adult patients with newly diagnosed AL amyloidosis for whom VCd is the best suited ACT, a hint of minor added benefit of daratumumab was found in comparison with individualized therapy, taking into account general health, comorbidity, and organ deterioration.

Patients for whom a therapy other than VCd is the best suited ACT

The company did not present any data on adult patients with newly diagnosed systemic AL amyloidosis for whom a therapy other than VCd is the best suited ACT. For these patients, there is consequently no hint of added benefit of daratumumab in comparison with individualized

therapy, taking into account general health, comorbidity, and organ deterioration; added benefit is therefore not proven.

The result of the assessment of the added benefit of daratumumab in combination with VCd in comparison with the ACT is summarized in Table 18.

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

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Treatment of adult patients with newly diagnosed systemic lightchain amyloidosis[b]	Individualized therapy, taking into account general health, comorbidity, and organ deterioration[c]	Patients for whom bortezomib + cyclophosphamide + dexamethasone is best suited: hint of minor added benefit
		Patients for whom a therapy other than bortezomib + cyclophosphamide + dexamethasone is best suited: added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. In principle, the therapeutic indication includes patients eligible for immediate stem cell transplantation.
c. No drug therapies have been approved for the treatment of light-chain amyloidosis. For individualized therapy, the following therapies are deemed suitable comparators within clinical trials: bortezomib + cyclophosphamide + dexamethasone, bortezomib ± dexamethasone, bortezomib + melphalan + dexamethasone, lenalidomide + cyclophosphamide + dexamethasone, lenalidomide + dexamethasone, melphalan + dexamethasone, lenalidomide + melphalan + dexamethasone. As part of individualized therapy for eligible patients, the ACT also includes high-dose melphalan therapy with subsequent autologous stem cell transplantation. The latter can be indicated either immediately or following induction therapy.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; VCd: bortezomib + cyclophosphamide + dexamethasone

The above-described assessment departs from the conclusion drawn by the company in that the company derived an indication of considerable added benefit for adult patients with newly diagnosed systemic AL amyloidosis who are eligible for VCd treatment in consideration of general health, comorbidity, and organ deterioration.

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

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Please see full dossier assessment for full reference list.

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