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

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 (neu diagnostiziertes multiples Myelom, Stammzelltransplantation geeignet) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 May 2020). 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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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ASCT	autologous stem cell transplantation
D-VTd	daratumumab + bortezomib + thalidomide + dexamethasone
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IMWG	International Myeloma Working Group
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PFS	progression-free survival
RCT	randomized controlled trial
sCR	stringent complete response
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
VTd	bortezomib + thalidomide + dexamethasone

2 Benefit assessment

2.1 Extract of dossier 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 bortezomib, thalidomide, and dexamethasone. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 17 February 2020.

Research question

This report aims to assess the added benefit of daratumumab in combination with bortezomib, thalidomide, and dexamethasone in comparison with the appropriate comparator therapy (ACT) cell transplantation (ASCT).

The G-BA's ACT is presented in Table 2.

Table 2: Research questions of the benefit assessment of daratumumab in combination with bortezomib, thalidomide, and dexamethasone

Research question	Indication	ACT[a]
1	Adult patients with newly diagnosed multiple myeloma who are eligible for ASCT	▪ Induction therapy consisting of bortezomib-dexamethasone-based triple combination therapy upon the physician's discretion[b], followed by ▪ high-dose therapy with melphalan and subsequent autologous stem cell transplantation, followed by ▪ maintenance therapy consisting of: lenalidomide

a. Presented is the respective ACT specified by the G-BA.
b. With regard to the induction therapy, there is a discrepancy between the drugs approved for the indication versus those recommended in the guidelines. In the context of a clinical study, the following combination therapies technically constitute suitable comparators: bortezomib + thalidomide + dexamethasone as well as bortezomib + cyclophosphamide + dexamethasone. Bortezomib in combination with cyclophosphamide and dexamethasone is not approved for this indication.

ACT: appropriate comparator therapy; ASCT: autologous stem cell transplantation; G-BA: Federal Joint Committee

The company followed the G-BA's specification and purported to present data for a comparison with bortezomib in combination with thalidomide and dexamethasone.

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

Study pool of the company

To assess any added benefit of daratumumab in combination with bortezomib, thalidomide, and dexamethasone, the company used the RCT CASSIOPEIA. This study is not suitable for

deriving an added benefit of daratumumab in combination with bortezomib, thalidomide, and dexamethasone in comparison with the ACT. The reason is explained below:

The treatment phase of the CASSIOPEIA study comprises 2 parts:

- Part 1 – Induction therapy with four 28-day cycles of daratumumab + bortezomib + thalidomide + dexamethasone (D-VTd) or bortezomib + thalidomide + dexamethasone (VTd), high-dose therapy followed by ASCT, consolidation therapy with a further 2 cycles of D-VTd or VTd.
- Part 2 – Either maintenance therapy with daratumumab or monitoring without therapy

Part 1 of the CASSIOPEIA study implements the ACT including ASCT in the comparator arm. Part 1 of the study is unsuitable for deriving an added benefit since it does not represent the complete first-line therapy. Part 2 of the study investigates maintenance therapy. In this part, patients are rerandomized into a daratumumab monotherapy group or a monitoring without therapy group. Consequently, patients of both treatment arms from part 1 receive either daratumumab or no further treatment in part 2 of the study. The maintenance therapy therefore does not implement the ACT of lenalidomide; in addition, due to rerandomization, the original randomizationis not preserved. Part 2 of the study is therefore not suitable for deriving an added benefit in comparison with the ACT of lenalidomide in maintenance therapy.

Results

The company's dossier did not present any data suitable for assessing daratumumab in combination with bortezomib, thalidomide, and dexamethasone in adult patients with newly diagnosed multiple myeloma who are eligible for ASCT. Hence, it is not possible to derive a hint of added benefit of daratumumab in combination with bortezomib, thalidomide, and dexamethasone in comparison with the ACT. An added benefit is therefore not proven.

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 in combination with bortezomib, thalidomide, and dexamethasone in comparison with the ACT are assessed as follows:

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

Table 3 presents a summary of the probability and extent of added benefit of daratumumab in combination with bortezomib, thalidomide, and dexamethasone.

Table 3: Daratumumab in combination with bortezomib, thalidomide, and dexamethasone – probability and extent of added benefit

Indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplantation[b]	▪ Induction therapy consisting of bortezomib-dexamethasone-based triple combination therapy upon the physician's discretion[c], followed by ▪ high-dose therapy with melphalan and subsequent ASCT, followed by ▪ maintenance therapy consisting of: lenalidomide	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. The CASSIOPEIA study included patients only up to 65 years of age. It remains unclear whether the observed effects translate to patients older than 65 years.
c. For the induction therapy, there is a discrepancy between the drugs approved for the indication and those recommended in the guidelines. In the context of a clinical study, the following combination therapies technically constitute suitable comparators: bortezomib + thalidomide + dexamethasone as well as bortezomib + cyclophosphamide + dexamethasone. Bortezomib in combination with cyclophosphamide and dexamethasone is not approved for this indication.

ACT: appropriate comparator therapy; ASCT: autologous stem cell transplantation; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

2.2 Research question

This report aims to assess the added benefit of daratumumab in combination with bortezomib, thalidomide, and dexamethasone in comparison with the ACT in adult patients with newly diagnosed multiple myeloma who are eligible for ASCT.

The G-BA's ACT is presented in Table 4.

Table 4: Research question of the benefit assessment of daratumumab in combination with bortezomib, thalidomide, and dexamethasone

Research question	Indication	ACT[a]
1	Adult patients with newly diagnosed multiple myeloma who are eligible for ASCT	▪ Induction therapy consisting of bortezomib-dexamethasone-based triple combination therapy upon the physician's discretion[b], followed by ▪ high-dose therapy with melphalan and subsequent ASCT, followed by ▪ maintenance therapy consisting of: lenalidomide

a. Presented is the respective ACT specified by the G-BA.
b. With regard to the induction therapy, there is a discrepancy between the drugs approved for the indication versus those recommended in the guidelines. In the context of a clinical study, the following combination therapies technically constitute suitable comparators: bortezomib + thalidomide + dexamethasone as well as bortezomib + cyclophosphamide + dexamethasone. Bortezomib in combination with cyclophosphamide and dexamethasone is not approved for this indication.

ACT: appropriate comparator therapy; ASCT: autologous stem cell transplantation; G-BA: Federal Joint Committee

The company followed the G-BA's specification and purported to present data for a comparison with bortezomib in combination with thalidomide and dexamethasone.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used for deriving any added benefit. This coincides 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 of the company in the dossier:

- Study list on daratumumab (status: 15 January 2020)
- Bibliographic literature search on daratumumab (most recent search on 15 January 2020)
- Search in trial registries / study results databases on daratumumab (most recent search on 15 January 2020)
- Search on the G-BA website for daratumumab (most recent search on 15 January 2020)

To check the completeness of the study pool:

- Search in trial registries for studies on daratumumab (most recent search on 02 March 2020)

The check did not identify any additional relevant study.

Study pool of the company

To assess any added benefit of daratumumab in combination with bortezomib, thalidomide, and dexamethasone, the company used the RCT CASSIOPEIA [3-7]. This study is not suitable for deriving an added benefit of daratumumab in combination with bortezomib, thalidomide, and dexamethasone in comparison with the ACT. The reason is explained below.

CASSIOPEIA study

The characteristics of the CASSIOPEIA study are presented in Appendix A of the full dossier assessment.

The CASSIOPEIA study is an open-label, randomized, actively controlled study comparing D-VTd with VTd. Adult patients with newly diagnosed multiple myeloma who were eligible for high-dose chemotherapy and ASCT while not being older than 65 years of age were eligible for inclusion. In addition, patients had to have an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) ≤ 2.

In total, 1085 patients were randomized in a 1:1 ratio and allocated to the two treatment arms: 543 patients to the D-VTd arm and 542 patients to the VTd arm. The allocation was stratified by study groups (Intergroupe Frankophone du Myélome versus Hemato-Oncologie voor Volwassenen Nederland), by disease stage according to the International Staging System (ISS) (I versus II versus III), and by cytogenetics (standard versus high risk, defined as the presence of a del17p deletion or t(4;14) translocation, centrally captured at the time of screening).

Figure 1 presents a schematic diagram of the study design.

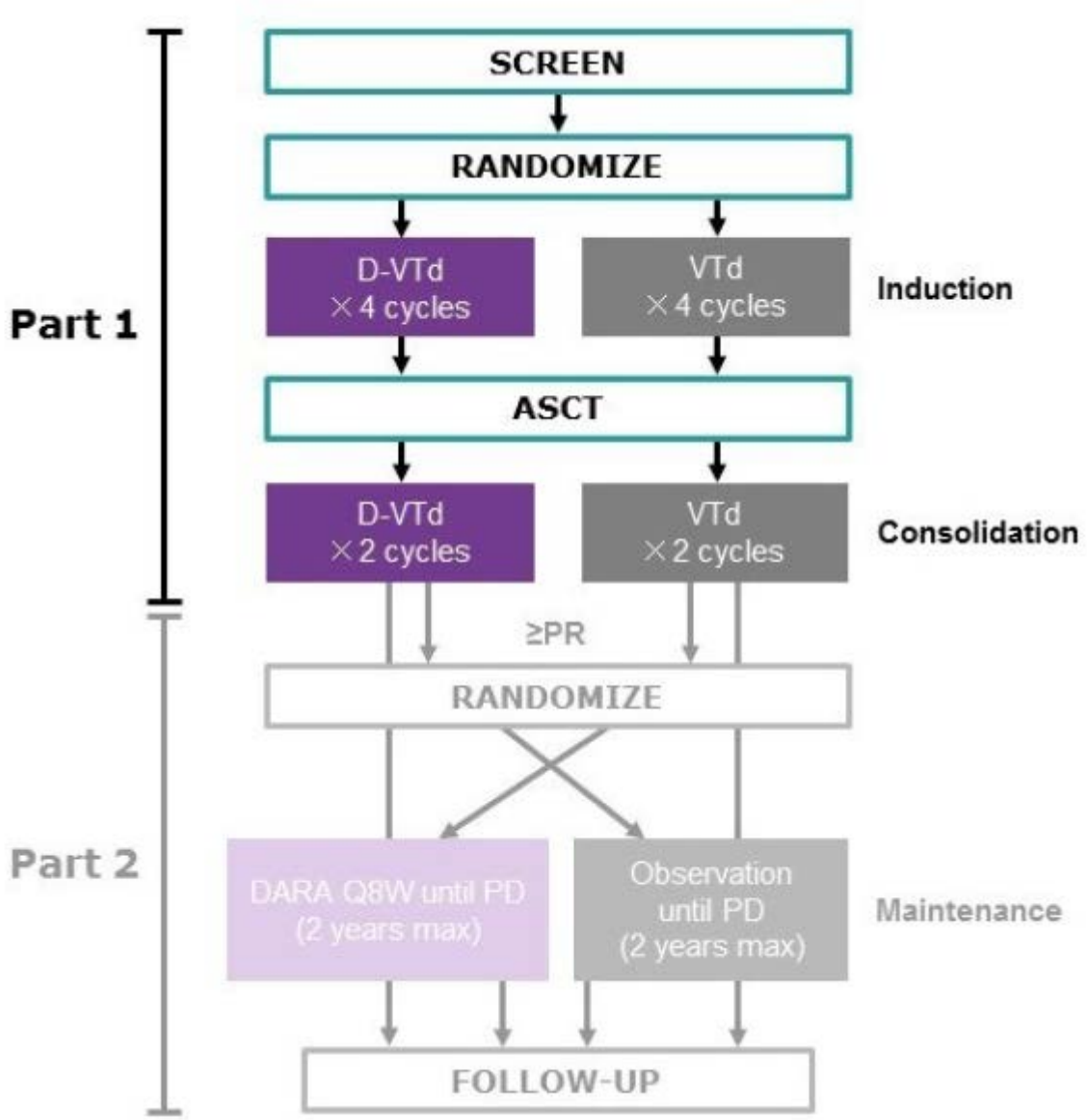

Figure 1: CASSIOPEIA study, schematic diagram of the study design

The treatment phase of the CASSIOPEIA study comprises 2 parts:

- Part 1 – Induction therapy, high-dose chemotherapy with subsequent ASCT, consolidation therapy:

Patients in both intervention arm and comparator arm initially received 4 cycles of induction therapy (each lasting 28 days) with D-VTd and VTd, respectively. Provided no disease progression was observed, this was followed by stem cell mobilization via the administration of cyclophosphamide and granulocyte colony-stimulating factor (G-CSF). In the present CASSIOPEIA study, 492 of 542 patients (91%) in the comparator arm and 506 of 543 patients (93%) in the daratumumab arm met the prerequisite for stem cell mobilization. Patients who the investigator deemed ineligible for stem cell mobilization or who exhibited disease

progression had to terminate treatment and were then monitored. After stem cell collection, patients received high-dose chemotherapy with 200 mg/m^2 melphalan. The stem cells were then reinfused. Stem cell transplantation was conducted in a total of 484 patients (89%) in the comparator arm and 489 patients (90%) in the intervention arm. At 30 to 60 days after stem cell transplantation, patients whom the physician deemed able to tolerate systemic follow-up therapy received 2 more cycles (each lasting 28 days) of consolidation therapy with the allocated treatment regimen (D-VTd or VTd). The primary outcome of part 1 was stringent complete response (sCR) after completion of consolidation therapy. This outcome was measured 100 days after stem cell transplantation or directly after the end of the consolidation therapy, whichever was later. The patient-relevant secondary outcomes of part 1 were overall survival, health status, symptoms, health-related quality of life, and adverse events.

- Part 2 – maintenance therapy:

For maintenance therapy in part 2 of the CASSIOPEIA study, patients who exhibited at least partial response in accordance with the criteria of the International Myeloma Working Group (IMWG) at the time point 100 days after stem cell transplantation were randomized in a 1:1 ratio after completing consolidation therapy and allocated to either daratumumab monotherapy or monitoring without further treatment for a period of no more than 2 years. The randomization was stratified by type of induction therapy (D-VTd versus VTd) and depth of response following induction and consolidation therapy (in accordance with minimum residual disease [MRD] status and response following consolidation). The primary outcome of this part 2 of the study is progression-free survival (PFS). This part of the study is still ongoing.

Follow-up

Patients who have completed treatment are followed up for a maximum of 5 years after the last patient started part 2 of the treatment phase or up to the point where 350 deaths have occurred.

Data cut-offs

The CASSIOPEIA study calls for 2 primary analyses, 1 each for part 1 and part 2 of the treatment phase. The primary and final analysis of part 1 was to be conducted when all patients had either undergone the response rating 100 days after stem cell transplantation or had discontinued treatment. The data cut-off for this analysis was 19 June 2018. The primary analysis of part 2 is to be conducted after 390 PFS events. A final data cut-off is predefined at the end of the study, after about 350 deaths or about 5 years after the last patient started part 2 of the treatment phase.

ACT not implemented in part 2 of the CASSIOPEIA study

As the ACT, the G-BA specified induction therapy consisting of bortezomib-dexamethasone-based triple combination therapy upon the physician's discretion, followed by high-dose melphalan therapy and subsequent ASCT, followed by lenalidomide maintenance therapy. Part 1 of the CASSIOPEIA study implements the ACT including ASCT in the comparator arm. Part 2 of the study investigates the subsequent maintenance therapy. In this part, patients are

rerandomized into either a daratumumab monotherapy group or monitoring without therapy group. Consequently, patients of both treatment arms in part 1 receive either daratumumab or no further treatment in part 2 of the study; in addition, rerandomization abandons the original randomized allocation. The ACT of lenalidomide is consequently not implemented in maintenance therapy. Part 2 of the study is therefore not suitable for deriving an added benefit in comparison with the ACT of lenalidomide in maintenance therapy.

Analyses presented by the company

To derive any added benefit, the company used daratumumab in combination with bortezomib, thalidomide, and dexamethasone in the primary analysis of part 1 of the treatment phase in the CASSIOPEIA study. However, this part of the treatment does not cover the entire therapy in the therapeutic indication. For newly diagnosed patients eligible for ASCT, first-line therapy consists of induction therapy, high-dose chemotherapy with ASCT, possibly consolidation, and maintenance therapy [8-10]. These therapies cannot be considered in isolation and must be viewed as 1 treatment line rather than consecutive treatment lines [8,9,11]. Part 1 of the CASSIOPEIA study therefore does not represent the complete first-line therapy, and the consideration of results without maintenance therapy and further follow-up is inappropriate. Part 1 of the CASSIOPEIA study does show statistically significant effects, both in favour and to the disadvantage of daratumumab in combination with bortezomib, thalidomide, and dexamethasone compared to treatment with bortezomib, thalidomide, and dexamethasone. For instance, an advantage is found for the primary outcome of sCR 100 days after stem cell transplantation (as defined using IMWG criteria [11,12]); this advantage was determinative in the approval of daratumumab for the assessed therapeutic indication. It is unclear, however, to what extent patients experience a long-term impact from these advantages and disadvantages regarding patient-relevant outcomes, such as overall survival. Against this background and in view of the marketing authorization, the European Medicines Agency (EMA) asked for additional results from part 2 of the study. In its dossier, the company presents supplementary results from this data cut-off in part 2 of the study on the outcomes of overall survival, PFS, and time to progression. However, since part 2 of the CASSIOPEIA study is not suitable for deriving any added benefit in comparison with the ACT of lenalidomide (as maintenance therapy), the results of the additional data cut-off are not usable.

Other limitations of the CASSIOPEIA study

Exclusion of patients > 65 years of age

The CASSIOPEIA study included patients with a maximum age of 65 years and an ECOG-PS of 0, 1, or 2. Important eligibility criteria for ASCT are biological age with good organ function and the absence of other significant comorbidities [8]. Generally, chronological age alone is therefore not a limiting factor in determining whether ASCT is a suitable treatment option [9,10]. Rather, this decision is based on the patient's health status. Irrespective of the general suitability of the CASSIOPEIA study, the research question would be left unanswered for patients over 65 years of age.

Dosing regimen

The dosing of thalidomide in combination with bortezomib and dexamethasone is described in the Summary of Product Characteristics (SPC) of bortezomib [13]. Accordingly, in the 1st cycle, the thalidomide dosage is increased from 50 mg daily in weeks 1 and 2 to 100 mg in weeks 3 and 4. From cycle 2, the dose is increased to 200 mg, if tolerated. In the CASSIOPEIA study, in contrast, patients received a dose of 100 mg in all cycles. Overall, the thalidomide dose in the study is therefore lower than specified in the SPC.

The dosing of dexamethasone in combination with bortezomib and thalidomide is described in the bortezomib SPC as well [13]. Accordingly, in all cycles, 40 mg dexamethasone is administered on days 1, 2, 3, 4 and days 8, 9, 10, 11. In the CASSIOPEIA study, in contrast, patients in cycles 1 and 2 received 40 mg each on days 1, 2, 8, 9, 15, 16, 22, and 23. In cycles 3 and 4, patients received 40 mg on days 1 and 2, followed by 20 mg each on days 8, 9, 15, and 16. In cycles 5 and 6, 20 mg was administered on days 1, 2, 8, 9, 15, 16. Hence, the dexamethasone dose used in the CASSIOPEIA study is likewise lower overall than the one specified in the SPC.

As the principal reason for this modified dosing regimen, the company specifies the avoidance of peripheral neuropathies, referencing studies which suggest an improved tolerability profile at the same efficacy [14,15]. These studies, however, investigated drug combinations of bortezomib, thalidomide, and dexamethasone by comparing them with a combination of bortezomib, cyclophosphamide, and dexamethasone or with a drug combination of bortezomib, thalidomide, dexamethasone, and cyclophosphamide. The company did not submit a direct comparison between the approved dosages of bortezomib + thalidomide + dexamethasone in combination with in comparison with the dosing regimen used in the CASSIOPEIA study. Therefore, it remains unclear whether the efficacy and safety of the modified dosage regimen are comparable with those of the approved dosage regimen.

Summary

All things considered, no data suitable for answering the research question of this benefit assessment are available. This is due to the fact that, in its part 2 (maintenance therapy), the CASSIOPEIA study submitted by the company uses a comparator therapy which does not correspond to the ACT. Hence, no comparative data for the entire treatment sequence are available for assessing an added benefit of daratumumab in combination with bortezomib, thalidomide, and dexamethasone in comparison with the ACT.

2.4 Results on added benefit

The company's dossier does not present any suitable data for assessing an added benefit of daratumumab in combination with bortezomib, thalidomide, and dexamethasone in adult patients with newly diagnosed multiple myeloma who are eligible for ASCT. Hence, it is not possible to derive a hint of added benefit of daratumumab in combination with bortezomib,

thalidomide, and dexamethasone in comparison with the ACT. An added benefit is therefore not proven.

2.5 Probability and extent of added benefit

Since the company's dossier did not present any data suitable for assessing an added benefit of daratumumab in combination with bortezomib, thalidomide, and dexamethasone in comparison with the ACT for the therapeutic indication in question; an added benefit of daratumumab in combination with bortezomib, thalidomide, and dexamethasone is not proven.

Table 5 presents a summary of the results of the benefit assessment of daratumumab in combination with bortezomib, thalidomide, and dexamethasone in comparison with the ACT.

Table 5: Daratumumab in combination with bortezomib, thalidomide, and dexamethasone – probability and extent of added benefit

Indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplantation[b]	▪ Induction therapy consisting of bortezomib-dexamethasone-based triple combination therapy upon the physician's discretion[c], followed by ▪ high-dose therapy with melphalan and subsequent ASCT, followed by ▪ maintenance therapy consisting of: lenalidomide	Added benefit not proven
a. Presented is the respective ACT specified by the G-BA. b. The CASSIOPEIA study included patients only up to 65 years of age. It remains unclear whether the observed effects translate to patients older than 65 years. c. For the induction therapy, there is a discrepancy between the drugs approved for the indication and those recommended in the guidelines. In the context of a clinical study, the following combination therapies technically constitute suitable comparators: bortezomib + thalidomide + dexamethasone as well as bortezomib + cyclophosphamide + dexamethasone. Bortezomib in combination with cyclophosphamide and dexamethasone is not approved for this indication. ACT: appropriate comparator therapy; ASCT: autologous stem cell transplantation; G-BA: Federal Joint Committee		

This assessment deviates from that of the company, which purports a considerable added benefit for the above research question on the basis of the results of the CASSIOPEIA study.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

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

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The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a20-15-daratumumab-multiple-myeloma-stem-cell-transplant-benefit-assessment-according-to-35a-social-code-book-v.12976.html.