Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Daratumumab (New Therapeutic Indication: Multiple Myeloma, Newly Diagnosed, Patients Eligible for Autologous Stem Cell Transplant, Combination with Bortezomib, Thalidomide, and Dexamethasone)

of 20 August 2020

Contents

1. Legal basis

According to Section 35a, paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. Approved therapeutic indications,
2. Medical benefit,
3. Additional medical benefit in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. Treatment costs for statutory health insurance funds,
6. Requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient daratumumab was first placed on the German market on 1 June 2016.

Daratumumab is approved as a medicinal product for the treatment of rare diseases in accordance with Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999.

In its previously approved therapeutic indications, the sales of daratumumab within the German statutory health insurance system at pharmacy sales prices including VAT exceeded € 50 million, necessitating the submission of evidence for daratumumab in accordance with Section 5, paragraphs 1 to 6 of the Rules of Procedure (VerfO) of the G-BA to demonstrate its additional benefit compared with the appropriate comparator therapy.

On 20 January 2020, daratumumab received the marketing authorisation for a new therapeutic indication classified as a major type 2 variation according to Annex 2, number 2a to Regulation (EC) No. 1234/2008 of the Commission from 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12 December 2008, p. 7).

On 14 February 2020, the pharmaceutical company submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules

of Procedure (VerfO) of the G-BA on the active ingredient daratumumab with the new therapeutic indication (multiple myeloma, newly diagnoses, patients eligible for autologous stem cell transplant, combination with bortezomib, thalidomide, and dexamethasone) in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 15 May 2020, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of daratumumab compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has assessed the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods[1] was not used in the benefit assessment of daratumumab.

In the light of the above and taking into account the statements received and the oral hearing, the G-BA has arrived at the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of daratumumab (Darzalex ®) in accordance with the product information

Darzalex® is indicated in combination with bortezomib, thalidomide, and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant

- An induction therapy consisting of:
  a bortezomib-dexamethasone-based triple combination therapy according to the doctor's instructions
- Followed by high-dose therapy with melphalan and subsequent autologous stem cell transplant

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication according to the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal applications or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

On 1. Bortezomib in combination with dexamethasone or with dexamethasone and thalidomide is explicitly approved for induction treatment in the present therapeutic indication. In addition, the chemotherapeutic agents carmustine, cyclophosphamide, doxorubicin, melphalan, and vincristine, the immunostimulant interferon alfa-2b, and the glucocorticoids dexamethasone, prednisolone and prednisone are approved for the treatment of multiple myeloma.

On 2. In the present therapeutic indication, autologous and allogenic stem cell transplant are to be considered as non-medicinal treatments.

On 3. There is no resolution on the benefit assessment of medicinal products with new active ingredients (Section 35a SGB V).

A resolution of 18 October 2018 on the issue of mandates to the expert groups according to Section 35c, paragraph 1 SGB V is available:

- Bortezomib + cyclophosphamide + dexamethasone for the induction therapy of newly diagnosed multiple myeloma

There is a resolution of 19 January 2017 on the directive on methods of hospital treatment (status: 23 February 2018) – methods for which the evaluation procedures have been suspended:

- Autologous multiple transplant (tandem transplant) for multiple myeloma
- Allogeneic stem cell transplant for multiple myeloma in first-line therapy

On 4. From systematic reviews and relevant guidelines for the treatment of patients with newly diagnosed multiple myeloma, it can be concluded that patients are treated with induction therapy by default prior to autologous stem cell transplant. For the latter, there is a unanimous recommendation for a triple combination containing the two active ingredients bortezomib and dexamethasone. Related triple combinations for induction therapy are bortezomib in combination with thalidomide and dexamethasone, bortezomib in combination with cyclophosphamide, and dexamethasone and bortezomib in combination with lenalidomide and dexamethasone.

With regard to the authorisation status of the medicinal products concerned, only the triple combination of bortezomib with thalidomide and dexamethasone is approved. The triple combination of bortezomib, cyclophosphamide, and dexamethasone is not approved for this indication. Similarly, Bortezomib in combination with lenalidomide and dexamethasone is not approved for the induction therapy of newly diagnosed multiple myeloma in patients eligible for autologous stem cell transplant. For the triple combination consisting of bortezomib, lenalidomide, and dexamethasone, in its approval process for lenalidomide (Revlimid®) for the treatment of newly diagnosed multiple myeloma, the European Medicines Agency (EMA) concluded that for patients

eligible for autologous stem cell transplant, the evidence presented for marketing authorisation did not allow a conclusion to be reached on either superiority or non-inferiority to standard therapy.

By resolution of 18 October 2018, the G-BA commissioned the off-label expert groups to assess the state of scientific knowledge regarding the application of the combination therapies bortezomib + cyclophosphamide + dexamethasone for the induction therapy of newly diagnosed multiple myeloma.

Against this background, there is a discrepancy between the medicinal products authorised in the indication and those recommended in the guidelines. For induction therapy, an appropriate comparator therapy consisting of a triple combination therapy based on bortezomib-dexamethasone is determined according to the doctor's instructions. In the context of a clinical trial, the following combination therapies are basically equally suitable comparators: Bortezomib + thalidomide + dexamethasone as well as bortezomib + cyclophosphamide + dexamethasone.

The approved dual combination of bortezomib and dexamethasone is not considered an appropriate comparator therapy because of the unanimous recommendation for a triple combination in induction therapy.

The induction therapy is followed by a high-dose therapy with melphalan and subsequent autologous stem cell transplant. According to the evidence available, high-dose therapy with the active ingredient melphalan represents the standard in this regard.

A consolidating antineoplastic therapy following autologous stem cell transplant has so far not been able to show any advantage in terms of overall survival and cannot be regarded as standard based on the evidence available. Here, the concept of a "consolidating" therapy must be distinguished from that of a "maintenance treatment", which addresses different treatment goals.

Change of the appropriate comparator therapy:

The appropriate comparator therapy was originally determined as follows:

Adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant

- An induction therapy consisting of:
  a bortezomib-dexamethasone-based triple combination therapy according to the doctor's instructions
- Followed by high-dose therapy with melphalan and subsequent autologous stem cell transplant
- Followed by a maintenance treatment consisting of:
  lenalidomide

Because maintenance treatment is not part of the marketing authorisation extension, the maintenance treatment phase is not considered part of the appropriate comparator therapy.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment contract.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of daratumumab is assessed as follows:.

For daratumumab in combination with bortezomib, thalidomide, and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant, there is a hint for a non-quantifiable additional benefit.

Justification:

To prove the additional benefit, the pharmaceutical company has submitted data from the randomised, controlled CASSIOPEIA study. The CASSIOPEIA study consists of two parts.

Within Part 1, an induction therapy, followed by a high-dose therapy with subsequent autologous stem cell transplant (ASCT) and followed by a consolidation therapy is performed. Induction therapy in the control arm consists of four cycles of daratumumab + bortezomib + thalidomide + dexamethasone (D-VTd). In the comparator arm, four cycles of bortezomib + thalidomide + dexamethasone (VTd) are given as induction therapy. After stem cell mobilisation, high-dose chemotherapy with melphalan and autologous stem cell transplant, a consolidation therapy with four further cycles of the therapy regime already given in the induction phase is performed in both arms.

In Part 2 of the study, the maintenance phase takes place. In this respect, patients are once again randomised to two study arms after completion of the consolidation in Part 1. This involves stratification by type of induction therapy (D-VTd vs VTd) and depth of response after induction and consolidation therapy. In the test arm, maintenance treatment is performed with daratumumab; in the control arm, there is an observation phase without further treatment.

The pharmaceutical company presented the results of two data cut-offs.

To prove the additional benefit, the pharmaceutical company has submitted data from the randomised, controlled CASSIOPEIA study. The CASSIOPEIA study consists of two parts.

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In Part 2 of the study, the maintenance phase takes place. In this respect, patients are once again randomised to two study arms after completion of the consolidation in Part 1. This involves stratification by type of induction therapy (D-VTd vs VTd) and depth of response after induction and consolidation therapy. In the test arm, maintenance treatment is performed with daratumumab; in the control arm, there is an observation phase without further treatment. As a result, a medicinal product without marketing authorisation for maintenance treatment is used in the test arm with daratumumab. According to the current state of medical knowledge, the monitoring wait-and-see approach carried out in the comparator arm represents a sub-therapy in the present therapy situation and does not correspond to the therapy standard and lenalidomide as an appropriate comparator therapy for the maintenance phase as determined by the G-BA.

The marketing authorisation of the new therapeutic indication for daratumumab relates exclusively to the induction phase prior to autologous stem cell transplant in adult patients with newly diagnosed multiple myeloma as well as the subsequent consolidation phase. The maintenance phase is not part of the authorisation extension. Accordingly, only Part 1 of the study is considered in the present benefit assessment.

The pharmaceutical company submitted two data cut-offs. The evaluation of these data cut-offs is based on the randomisation for part 1 of the study. For the results on the overall survival endpoint, the problem for both data cut-offs is that a large proportion of the patients included have already been subjected to an inadequate maintenance treatment over a long period of time. It therefore remains unclear how overall survival would have developed under a guideline-based maintenance treatment. The transferability to the German healthcare context

is therefore uncertain. However, the re-randomisation for Part 2 means that it can be assumed that the results from maintenance treatment will not lead to the advantage or disadvantage of the test or control arm from Part 1. Moreover, the collection of data for the other endpoint categories morbidity, quality of life, and side effects had already been completed before the start of the maintenance phase. Against the background of these explanations, the data presented for Part 1 of the study can be used for the benefit assessment. However, because of the transition to the maintenance phase, there are uncertainties regarding the results for overall survival.

Extent and probability of the additional benefit

Mortality

In the CASSIOPEIA study, overall survival is operationalised as the time from randomisation to the occurrence of death by any cause.

For the endpoint overall survival, data from the 1st and 2nd data cut-off are available. At the time of the 1st data cut-off, the median observation time was 8.8 months in the verum arm and 18.9 months in the control arm. At the 2nd data cut-off, the median observation time was 29.3 months in the verum arm and 29.2 months in the control arm.

A statistically significant difference in favour of daratumumab in combination with bortezomib + thalidomide + dexamethasone (D-VTd) compared with bortezomib + thalidomide + dexamethasone (VTd) was observed at the time of both data cut-offs (1st data cut-off): Hazard ratio (HR): 0.43; [95% confidence interval (CI): 0.23; 0.80]; p value = 0.007; 2nd data cut-off HR: 0.52; [95% CI: 0.33; 0.85]. In both arms, only a small number of events occurred at these time points (1st data cut-off: n = 14 (2.6%) vs n = 32 (5.9%); 2nd data cut-off: n = 26 (4.8%) vs n = 48 (8.9%)).

The study thus shows a clearly positive effect under the daratumumab quadruple combination D-VTd. With regard to the results on the endpoint, there are uncertainties because of the transition of patients into the maintenance phase.

Morbidity

Progression-free survival

In the CASSIOPEIA study, from the 1st randomisation, the endpoint progression-free survival is operationalised as time from randomisation to the onset of disease progression in accordance with IMWG criteria or death.

There is a statistically significant difference between the two study arms at both the 1st and 2nd data cut-off. At the time of the 2nd data cut-off, 83 patients (15.3%) had experienced an event under daratumumab + bortezomib + thalidomide + dexamethasone compared with 151 patients (27.9%) under bortezomib + thalidomide + dexamethasone (HR: 0.49; [95% CI: 0.38; 0.65; p < 0.0001).

The PFS endpoint is a combined endpoint composed of endpoints of the “mortality” and “morbidity” categories. The endpoint component “mortality” is already surveyed via the endpoint “overall survival” as an independent endpoint. The morbidity component “disease progression” is surveyed according to IMWG criteria and thus not in a symptom-related manner but rather by means of laboratory parametric, imaging, and haematological procedures. Taking the aforementioned factors into consideration, there are differing opinions within the G-BA regarding the relevance for patients of the PFS endpoint. The overall statement on additional benefit remains unaffected.

Symptomatology

In the CASSIOPEIA study, the disease symptomology was operationalised as time to deterioration by ≥ 10 points using the symptom scales of the cancer-specific EORTC QLQ-

C30 questionnaire. Data were collected up to 100 days after implementation of the ASCT or up to the 2nd randomisation for Part 2 of the study.

With regard to the symptom scale “pain”, there was a statistically significant advantage in favour of the daratumumab quadruple combination. In the other symptom scales (“fatigue”, “nausea and vomiting”, “insomnia”, “loss of appetite”, “constipation”, “diarrhoea”), there is no statistically significant difference between the verum and control arm.

There is thus an advantage in terms of the endpoint “pain” in terms of symptomatology.

Health status

In the CASSIOPEIA study, health status was surveyed using the EQ-5D VAS (Visual Analogue Scale of the European Quality of Life Questionnaire - 5 Dimensions). Data were collected up to 100 days after implementation of the ASCT or up to the 2nd randomisation for Part 2 of the study. The pharmaceutical company presented responder analyses operationalised as time to deterioration by 7 or 10 points.

In the dossier assessment of the IQWiG, the analyses of mean differences were used. The responder analyses were also presented in the annex to the dossier assessment. There are no comments on the decision-making process regarding the inclusion of continuous analyses or responder analyses.

In the recent past, the IQWiG has not used the responder analyses because the study on which the derivation of the minimal important difference MID is based (Pickard et al., 2007) is no longer considered suitable by the IQWiG to prove the validity of the MID. This is justified by the fact that the work mentioned does not contain a longitudinal study to determine the MID, which is assumed in the current scientific discussion on deriving a valid MID.

Instead of responder analyses, the IQWiG used analyses of mean differences. In the analyses of the standardised mean differences, there was no statistically significant difference between the two treatment arms.

Because responder analyses based on a MID have general advantages for a clinical evaluation of effects compared with analysis of standardised mean differences and because the validation study in question has already been used in earlier assessments, the G-BA has decided to draw on responder analyses in the current assessment to determine the effects on health status.

In the responder analyses, there was no statistically significant difference between the two treatment arms.

There is therefore no advantage or disadvantage in terms of health status.

<u>Quality of life</u>

The health-related quality of life was operationalised as time to deterioration by ≥ 10 points using the functional scales of the cancer-specific EORTC QLQ-C30 questionnaire. Data were collected up to 100 days after implementation of the ASCT or up to the 2nd randomisation for Part 2 of the study.

There is a statistically significant advantage on the functional scale “global health status” in favour of daratumumab in combination with bortezomib, thalidomide, and dexamethasone compared with the triple combination of bortezomib, thalidomide, and dexamethasone. In the other functional scales (“physical function”, “role function”, “emotional function”, “cognitive function”, and “social function”), there is no statistically significant difference between the two therapy arms.

In the quality of life category, there is thus an advantage in terms of the “global health status” scale.

<u>Side effects</u>

Adverse events (AE) in total

The results for the “combined adverse events” endpoint are presented additionally.

In both study arms, nearly every patient suffered an adverse event (D-VTd: 535 patients (99.8%); VTd: 536 patients (99.6%).

Serious adverse events (SAE)

There is no statistically significant difference between the two treatment arms.

Severe adverse events (CTCAE grade ≥ 3)

With regard to the endpoint severe adverse events (CTCAE grade ≥ 3), there is no statistically significant difference between the verum and control arm.

Discontinuation because of AE

With regard to the endpoint discontinuation because of AE operationalised as discontinuation of at least one active ingredient component, there is no statistically significant difference between the two treatment arms.

Overall, there is therefore neither an advantage nor a disadvantage for the daratumumab quadruple combination in the side effects category.

Overall assessment/conclusion

For the assessment of the additional benefit of daratumumab in combination with bortezomib + thalidomide + dexamethasone compared with the triple combination bortezomib + thalidomide + dexamethasone, results are available from the open-label, randomised, controlled CASSIOPEIA study on the endpoint categories mortality, morbidity, health-related quality of life, and side effects. The marketing authorisation extension covers only the induction and consolidation phase but not maintenance treatment. Accordingly, only the results of part 1 of the study are considered.

Already at the time of the first data cut-off, a relevant proportion of patients switched to maintenance treatment (Part 2), which does not meet the standard of care in both arms. Although it is assumed that this will not bias the results between the two study arms and that results on overall survival will not be influenced by maintenance treatment until a later point in time, there are still relevant uncertainties regarding the endpoint overall survival. On the other hand, the survey of the other endpoints was completed before moving on to Part 2 of the study.

With regard to overall survival, a statistically significant, clearly positive effect in favour of the daratumumab quadruple combination is shown at the time of both the 1st and 2nd data cut-offs. However, a limiting factor is that there was only a small number of events at the time of the data cut-offs. Furthermore, the uncertainties described exist with regard to the transition to the maintenance phase.

With regard to the morbidity category, there is a statistically significant advantage of the daratumumab combination therapy with regard to the disease symptomology in the “pain” scale of the EORTC QLQ-C30. There is no statistically significant difference in health status surveyed using the EQ-5D VAS.

In terms of health-related quality of life, there is an advantage for the daratumumab quadruple combination in the “global health status” functional scale of the EORTC QLQ-C30 functional scales.

In the side effects category, there are no statistically significant differences in the endpoints serious AE, severe AE (CTCAE grade ≥ 3), and discontinuation because of AE.

Overall, there is thus a clearly positive effect under the daratumumab quadruple combination with regard to overall survival. However, because of the uncertainties outlined above, it is not possible to quantify the extent of this. In addition, daratumumab combination therapy has shown benefits in terms of morbidity and quality of life.

In the overall view, there is thus a non-quantifiable additional benefit for daratumumab in combination with bortezomib, thalidomide, and dexamethasone for the treatment (induction and consolidation) of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of the randomised, open-label, active controlled Phase III CASSIOPEIA study.

There are relevant uncertainties in that the data cut-offs were surveyed when it is assumed that all patients had already entered the maintenance phase in which a maintenance treatment that does not meet the standard of care is used. Although it is assumed that the results of the two study arms will not be biases because of re-randomisation and that effects of maintenance treatment are not expected until a later date, there are still relevant uncertainties in the interpretation of the study results.

There are also further uncertainties with regard to the consolidation therapy carried out. In accordance with the guidelines, a consolidation therapy carried out following an autologous stem cell transplant is not considered standard in the present therapeutic indication.

In the light of the above, the overall reliability of data of the additional benefit is classified as a "hint".

2.1.4 Summary of the assessment

This assessment refers to the benefit assessment of a new therapeutic indication for the active ingredient daratumumab:

The therapeutic indication assessed here is as follows: Daratumumab is indicated in combination with bortezomib, thalidomide, and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant.

Daratumumab has received marketing authorisation as an orphan drug.

The appropriate comparator therapy was determined by the G-BA as follows:

- an induction therapy consisting of: a bortezomib-dexamethasone-based triple combination therapy according to the doctor's instructions
- followed by high-dose therapy with melphalan and subsequent autologous stem cell transplant

The pharmaceutical company presented results of the CASSIOPEIA RCT. Part 1 of the study compared the regime daratumumab + bortezomib + thalidomide + dexamethasone (D-VTd) with the regime bortezomib + thalidomide + dexamethasone (VTd) in the induction and consolidation phase. In Part 2 of the study, the re-randomisation of patients from Part 1 is followed by a maintenance phase consisting of daratumumab or a monitoring wait-and-see approach.

The marketing authorisation covers only the induction and consolidation phase and not the maintenance treatment. Accordingly, Part 1 of the study can be used to assess the additional benefit, irrespective of the maintenance treatment does not meet the standard of care in Part 2 of the study. It can be assumed that for the collection of data on overall survival at the 2nd data cut-off, all patients have already switched to maintenance treatment. However, it is assumed that: 1) no bias effect occurs between the two treatment arms as a result of re-randomisation and 2) overall effects on overall survival occur only much later because of the maintenance treatment. However, there are still relevant uncertainties in the assessment.

For the overall survival endpoint, there is a clear positive effect of the combination therapy D-VTd. However, because of the considerable uncertainties, it is not possible to quantify the extent of this.

In the morbidity category, there is an advantage for D-VTd in terms of the symptom “pain”. There is no difference in terms of health status.

With regard to the quality of life category, there is also a statistically significant difference in favour of D-VTd.

In the side effects category, there is no difference between serious AE, severe AE (CTCAE grade ≥ 3) and discontinuation because of AE.

There are thus overall benefits in terms of overall survival, disease symptoms, and health-related quality of life. Because of the relevant uncertainties described above, the extent of the benefit in overall survival cannot be quantified.

In the overall view, there is a hint for a non-quantifiable additional benefit.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The resolution will be based on the patient numbers from the dossier of the pharmaceutical company. Overall, the derivation is subject to uncertainties. However, the comparison carried out by the pharmaceutical company between the calculated number of patients eligible for ASCT and the transplants recorded in the German Registry for Stem Cell Transplants shows that the number of patients is within a plausible range.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Darzalex® (active ingredient: daratumumab) at the following publicly accessible link (last access: 7 May 2020):

https://www.ema.europa.eu/en/documents/product-information/darzalex-epar-product-information_de.pdf

Treatment with daratumumab should be initiated and monitored only by specialists in internal medicine, haematology, and oncology who are experienced in the treatment of patients with multiple myeloma.

In accordance with the specifications of the European Medicines Agency (EMA) regarding additional measures for risk minimisation, the pharmaceutical company must provide training material as well as a patient identification card. Training materials for healthcare professionals and blood banks include instructions on how to deal with the risks of interference with blood grouping caused by daratumumab (indirect anti-human globulin test or Coombs test). Daratumumab-induced interference with blood grouping may persist for up to six months after the last infusion of the medicinal product; healthcare professionals should therefore advise patients to carry their patient ID card for up to six months after the end of treatment.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 July 2020).

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit “days” is used to calculate the “number of treatments/patient/year”, the time between individual treatments, and the maximum treatment duration if specified in the product information.

For dosages depending on body weight (BW) or body surface, the average body measurements were used as a basis (average body size: 1.72 m, average body weight: 77 kg). From this, a body surface area of 1.90 m² is calculated (calculation according to Du Bois 1916)[2].

The annual treatment costs shown refer to the first year of treatment.

[2] German Federal Office For Statistics, Wiesbaden 2018: https://www.destatis.de/DE/Themen/Gesellschaft-Umwelt/Gesundheit/Gesundheitszustand-Relevantes-Verhalten/Publikationen/Downloads-Gesundheitszustand/koerpermasse-5239003179004.pdf?__blob=publicationFile

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Medicinal product to be assessed				
Daratumumab	28 day cycle: Week 1 – 8: every 7 days, Week 9–16, every 14 days	4	Cycle 1–2: 4 Cycle 3–4: 2	12
Bortezomib	On Day 1, 4, 8, and 11 of a 28-day cycle	4	4	16
Thalidomide	Day 1–28 of a 28-day cycle	4	28	112
Dexamethasone[3]	Cycle 1–2: Day 1, 2, 8, 9, 15, 16, 22, and 23	2	4	8
	Cycle 3–4: Day 1, 2, 8, 9, 15, 16,	2	4	8
High-dose chemotherapy with melphalan and autologous stem cell transplant				
	one-time			
Consolidation				
Daratumumab	28 day cycle: Week 1 – 8: every 14 days	2	2	4
Bortezomib	On Day 1, 4, 8, and	2	4	8

[3] On the days of the daratumumab infusion, the dose of dexamethasone was administered intravenously as pre-medication.

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
	11 of a 28-day cycle			
Thalidomide	Day 1–28 of a 28-day cycle	2	28	56
Dexamethasone[3]	1, 2, 8, 9, 15, and 16 of a 28-day cycle	2	4	8
Appropriate comparator therapy				
Induction therapy: Bortezomib-dexamethasone-based triple combination therapy according to the doctor's instructions[a]				
Bortezomib, thalidomide, dexamethasone				
Bortezomib	On Day 1, 4, 8, and 11 of a 28-day cycle	4 – 6	4	16 – 24
Thalidomide	Day 1–28 of a 28-day cycle	4 – 6	28	112 – 168
Dexamethasone	Day 1, 2, 3, 4, 8, 9, 10, and 11 of a 28-day cycle	4 – 6	8	32 – 48
High-dose chemotherapy with melphalan and autologous stem cell transplant				
	one-time			
[a] In addition to the combination therapy bortezomib + thalidomide + dexamethasone (VTD) listed, the triple combination bortezomib + cyclophosphamide + dexamethasone (VCD) also represents a suitable comparator for the present benefit assessment in the context of induction therapy according to the doctor's instructions. The costs are not shown because this triple combination is not approved in the present therapeutic indication.				

Usage and consumption:

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Daratumumab	16 mg/kg = 1,232 mg	1,232 mg	1 × 1,800 mg	12	12 × 1,800 mg
Bortezomib	1.3 mg/m^2	2.5 mg	1 × 2.5 mg	16	16 × 2.5 mg
Thalidomide	100 mg	100 mg	2 × 50 mg	112	224 × 50 mg
Dexamethasone[3]	Cycles 1–2 and Cycles 3–4, Day 1–2: 40 mg	40 mg	1 × 40 mg	Cycles 1–2: 8 Cycles 3–4: 2	10 × 40 mg
Dexamethasone[3]	Cycles 3–4 Day 8, 9, 15, 16: 20 mg	20 mg	1 × 20 mg	6	6 × 20 mg
High-dose chemotherapy with melphalan and autologous stem cell transplant					
	one-time				
Consolidation					
Daratumumab	16 mg/kg = 1,232 mg	1,232 mg	1 × 1,800 mg	4	4 × 1,800 mg
Bortezomib	1.3 mg/m^2	2.5mg	1 × 2.5 mg	8	8 × 2.5 mg
Thalidomide	100 mg	100 mg	2 × 50 mg	56	112 × 50 mg
Dexamethasone[3]	20 mg	20 mg	1 × 20 mg	8	8 × 20 mg
Appropriate comparator therapy					
An induction therapy consisting of: a bortezomib-dexamethasone-based triple combination therapy according to the doctor's instructions[a]					
Bortezomib, thalidomide, dexamethasone					
Bortezomib	1.3 mg/m^2	2.5 mg	1 × 2.5 mg	16 – 24	16 – 24 × 2.5 mg

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Thalidomide	Cycle 1: 50 mg on Day 1–14, 100 mg on Day 15–28; Cycle 2–6: 200 mg	50 – 200 mg	1 × 50 mg to 4 × 50 mg	112 – 168	378 – 602 × 50 mg
Dexamethasone	40 mg	40 mg	1 × 40 mg	32 – 48	32 – 48 × 40 mg
High-dose chemotherapy with melphalan and autologous stem cell transplant					
	one-time				
[a] In addition to the combination therapy bortezomib + thalidomide + dexamethasone (VTD) listed, the triple combination bortezomib + cyclophosphamide + dexamethasone (VCD) also represents a suitable comparator for the present benefit assessment in the context of induction therapy according to the doctor's instructions. The costs are not shown because this triple combination is not approved in the present therapeutic indication.					

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Sections 130 and 130 a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal product:

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Daratumumab 1800 mg	1 SFI	€ 6145.56	€ 1.77	€ 356.77	€ 5787.02
Bortezomib 2.5 mg	1 PIJ	€ 1116.94	€ 1.77	€ 53.85	€ 1,061.32
Thalidomide 50 mg	28 HC	€ 500.64	€ 1.77	€ 28.75	€ 470.12

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Dexamethasone 40 mg[4]	10 TAB	€ 44.86	€ 1.77	€ 0.00	€ 43.09
Dexamethasone 20 mg[4]	20 TAB	€ 52.46	€ 1.77	€ 0.00	€ 50.69
High-dose chemotherapy with melphalan and autologous stem cell transplant[5]					Costs: € 15,987.95 + 3,182.87
Appropriate comparator therapy					
Bortezomib 2.5 mg	1 PIJ	€ 1116.94	€ 1.77	€ 53.85	€ 1,061.32
Thalidomide 50 mg	28 HC	€ 500.64	€ 1.77	€ 28.75	€ 470.12
Dexamethasone 40 mg[4]	50 TAB	€ 183.02	€ 1.77	€ 0.00	€ 181.25
High-dose chemotherapy with melphalan and autologous stem cell transplant[5]					Costs: € 15,987.95 + 3,182.87
Abbreviations: HC = hard capsules; SFI = solution for injection; PIJ = powder for the preparation of an injection solution; TAB = tablets					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 July 2020

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be assessed and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary medical treatment or the prescription of other services when using the medicinal product to be assessed and the appropriate comparator therapy according to the product information, no costs for additionally required SHI services had to be taken into account.

[4] Fixed reimbursement rate
[5] DRG A15D + A42C Basic remuneration; Last updated: July 2020 (Source: https://www.drg-research-group.de/index.php)

Designation of the therapy	Package size	Costs (pharmacy selling price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/year	Costs/patient/year
Medicinal product to be assessed: Daratumumab in combination with bortezomib, thalidomide, and dexamethasone)							
Dexamethasone 40 mg i.v. (Cycles 1 – 2, Cycles 3 – 4 Day 1 – 2)[4]	1 × 40 mg SFI	€ 27.27	€ 1.77	€ 1.28	€ 24.22	10	€ 242.20
Dexamethasone 20 mg i.v. (Cycles 3 – 4, Day 8, 9, 15,16; Cycles 5 – 6)[4]	5 × 4 mg SFI	€ 13.63	€ 1.77	€ 0.23	€ 11.63	6	€ 69.78
Paracetamol 500 – 1,000 mg[4]	20 × 500 mg TAB	€ 1.46	€ 0.07	€ 0.06	€ 1.33	16	€ 1.33 – 2.66
Dimetindene i.v. 1 mg/10 kg	5 × 4 mg SFI	€ 18.15	€ 1.77	€ 1.92	€ 14.46	16	€ 101.22
Abbreviations: SFI = solution for injection; TAB = tablets							

Other services covered by SHI funds:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe; contract on price formation for substances and preparations of substances) is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131, paragraph 4 SGB V is a suitable basis for a standardised calculation.
According to the special agreement on contractual unit costs of retail pharmacist services [Hilfstaxe"] (last revised: 11. Supplementary Agreement of 1 March 2020 to the contract on price formation for substances and preparations of substances), surcharges for the preparation of parenteral preparations containing cytostatics of a maximum of € 81 per ready-to-use preparation and for the preparation of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit shall apply. These additional costs are not added to the pharmacy sales price but rather follow the rules for calculating the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredients, the invoicing of discards, and the calculation of application containers and carrier solutions according to the regulations of Annex 3 of the Hilfstaxe.

3. Bureaucratic costs

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 25 June 2019, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 14 February 2020, the pharmaceutical company submitted a dossier for the benefit assessment of daratumumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2, sentence 2 VerfO.

By letter dated 17 February 2020 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient daratumumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 May 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 15 May 2020. The deadline for submitting written statements was 5 June 2020.

The oral hearing was held on 22 June 2020.

By letter dated 23 June 2020, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 16 July 2020.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 28 July 2020, and the proposed resolution was approved.

At its session on 20 August 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	25 June 2019	Determination of the appropriate comparator therapy
Working group Section 35a	17 June 2020	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	22 June 2020	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents

Working group Section 35a	30 June 2020; 14 July 2020; 21 July 2020	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee on Medicinal Products	28 July 2020	Concluding discussion of the draft resolution
Plenum	20 August 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 20 August 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken