Ciltacabtagene autoleucel (multiple myeloma)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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

Patient and family involvement

The questionnaire on the disease and its treatment was answered by Hans Josef van Lier.

IQWiG thanks the respondent and Plasmozytom / Multiples Myelom NRW for participating in the written exchange about how they experienced the disease and its treatment and about the treatment goals. The respondent and Plasmozytom / Multiples Myelom NRW were not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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

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I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	Adverse event
CAR	chimeric antigen receptor
CD	cluster of differentiation
CTCAE	Common Terminology Criteria for Adverse Events
DKd	daratumumab in combination with carfilzomib and dexamethasone
DPd	daratumumab in combination with pomalidomide and dexamethasone
ECOG PS	Eastern Cooperative Oncology Group-Performance Status
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EPd	elotuzumab in combination with pomalidomide and dexamethasone
FDA	Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IMWG	International Myeloma Working Group
IQWiG	Institute for Quality and Efficiency in Health Care
IsaKd	isatuximab in combination with carfilzomib and dexamethasone
ISS	International Staging System
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model repeated measures
MySIm-Q	Multiple Myeloma Symptom and Impact Questionnaire
PFS	progression-free survival
PGIS	Patient Global Impression of Severity
PRO-CTCAE	Patient-Reported Outcomes version of the CTCAE
PT	Preferred Term
PVd	pomalidomide in combination with bortezomib and dexamethasone
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Social Code Book
SMQ	Standardized MedDRA Query

Abbreviation	Meaning
SOC	System Organ Class
SPC	Summary of Product Characteristics
VAS	visual analogue scale

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) has commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug ciltacabtagene autoleucel. 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 29 November 2024. Ciltacabtagene autoleucel

The drug in question is a drug for the treatment of an orphan disease and was approved in its first approval for the treatment of relapsed and refractory multiple myeloma in adult patients who have previously received at least 3 therapies, including 1 immunomodulator, 1 proteasome inhibitor and 1 anti-cluster of differentiation (CD) 38 antibody, and who showed disease progression during the last therapy. The decision of the G-BA on the benefit assessment procedure for the therapeutic indication of the first approval of ciltacabtagene autoleucel was limited. Within this time limit, the therapeutic indication of ciltacabtagene autoleucel was expanded and adjusted to patients who had received at least one prior therapy, including 1 immunomodulator and 1 proteasome inhibitor, who had demonstrated disease progression during the last therapy, and who were refractory to lenalidomide. This means that the previous therapeutic indication is covered by the new therapeutic indication. In addition, the turnover of the drug with the statutory health insurance had meanwhile exceeded the amount of € 30 million in the previous 12 calendar months. Following the temporary suspension of the procedure, the company was requested by the G-BA to submit a dossier on the added benefit versus the appropriate comparator therapy (ACT), which covers the entire therapeutic indication and forms the basis for the present assessment.

Research question

The aim of the present report is to assess the added benefit of ciltacabtagene autoleucel compared with an individualized treatment as ACT in adult patients with relapsed and refractory multiple myeloma who have previously received at least 1 therapy, including 1 immunomodulator and 1 proteasome inhibitor, and who have experienced disease progression during the last therapy and are refractory to lenalidomide.

The research question presented in Table 2 results from the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of ciltacabtagene autoleucel (multipage table)

Therapeutic indication	**ACT**[a]
Adults with relapsed and refractory multiple myeloma, who have received at least one prior therapy, including 1 immunomodulator and 1 proteasome inhibitor, who have demonstrated disease progression on the last therapy, and who are refractory to lenalidomide	Individualized treatment[b, c] choosing from ▪ daratumumab in combination with bortezomib and dexamethasone ▪ daratumumab in combination with carfilzomib and dexamethasone ▪ daratumumab in combination with pomalidomide and dexamethasone ▪ isatuximab in combination with carfilzomib and dexamethasone ▪ isatuximab in combination with pomalidomide and dexamethasone[d] ▪ elotuzumab in combination with pomalidomide and dexamethasone[d] ▪ pomalidomide in combination with bortezomib and dexamethasone[e] ▪ pomalidomide in combination with dexamethasone[f, g] ▪ carfilzomib in combination with dexamethasone ▪ panobinostat in combination with bortezomib and dexamethasone[f] ▪ bortezomib in combination with pegylated liposomal doxorubicin[f, g] ▪ bortezomib in combination with dexamethasone[f, g] ▪ daratumumab monotherapy[f, h] ▪ cyclophosphamide as monotherapy or in combination with dexamethasone[f, h] ▪ melphalan as monotherapy or in combination with prednisolone or prednisone[f, h] ▪ high-dose therapy with autologous stem cell transplantation[i] ▪ high-dose therapy with allogeneic stem cell transplantation[j, k] ▪ taking into account the general condition, the drugs and drug combinations used in the prior therapies as well as the type and duration of response to the respective prior therapies and the eligibility for stem cell transplantation[l, m]

Table 2: Research question for the benefit assessment of ciltacabtagene autoleucel (multipage table)

Therapeutic indication	ACT[a]
a. Presented is the ACT specified by the G-BA. b. For the implementation of individualized treatment in a study of direct comparison, the investigators are expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons). c. According to the G-BA, the duration of response to the prior therapy is a criterion for the individualized treatment. In this respect, according to the generally recognized state of medical knowledge, unsuitability of retreatment with the drugs or drug combinations of the prior therapy is defined as disease progression under the respective prior therapy or a duration of response of less than 12 months after completion of the respective prior therapy. Accordingly, for patients with relapsed disease who show a response in the form of CR, VGPR and PR of more than 12 months after completion of the prior therapy, treatment using the drugs or drug combinations used in the prior therapy may also be a suitable treatment option. d. Only for patients with at least 2 prior therapies. e. Only for patients who are refractory to a CD38 antibody. f. Only for patients who have received at least 4 prior therapies. g. Only for at least double-refractory patients for whom triplet therapy is not suitable. h. Only for at least triple-refractory patients for whom triplet or doublet therapy is not suitable. i. Only for patients after 1 prior therapy for whom autologous stem cell transplantation is an option; after achieving remission. Autologous stem cell transplantation should be offered to all patients eligible for transplantation who have not undergone transplantation as part of first-line therapy. In addition, an autologous re-transplantation can be performed if the progression-free survival after the first transplantation generally lasted at least 18 months. j. Only for patients after 1 prior therapy for whom allogeneic stem cell transplantation is an option; after achieving remission. Allogeneic stem cell transplantation is a treatment option for patients with primary refractoriness and an early relapse after autologous stem cell transplantation. k. The requirements of the "G-BA guideline on the testing of allogeneic stem cell transplantation in multiple myeloma beyond first-line therapy", the "G-BA's decision on measures of quality assurance for allogeneic stem cell transplantation in multiple myeloma (QS-B SZT MM)" and §137c of the German Social Code Book V shall apply with regard to the use of allogeneic stem cell transplantation. l. According to the G-BA, unsuitability of triplet or doublet therapy should be justified based on refractoriness and comorbidity of the patients and taking into account the toxicity of the respective therapy. m. According to the G-BA, patients in the present therapeutic indication are assumed to generally continue antineoplastic treatment. Best supportive care is therefore not considered an ACT. CD: cluster of differentiation; CR: complete response; G-BA: Federal Joint Committee; PR: partial response; SGB: Social Code Book; VGPR: very good partial response	

The G-BA adjusted the ACT after submission of the dossier on 7 January 2025, as shown in Table 2. In its dossier, the company uses the ACT from the procedure on idecabtagene vicleucel to derive the ACT. The resulting definition of the comparator therapy by the company largely corresponds to the current ACT of the G-BA of 7 January 2025. In deviation from this, however, the company does not name high-dose therapy followed by autologous stem cell transplantation and high-dose therapy followed by allogeneic stem cell transplantation as treatment options within the framework of individualized treatment. However, this deviation

has no consequences for the benefit assessment, as it has no impact on the completeness of the study pool. The present assessment is conducted on the basis of the ACT specified by the G-BA.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) are used to derive the added benefit.

Study pool and study design

The CARTITUDE-4 study was included for the benefit assessment.

Study design

The CARTITUDE-4 study is an ongoing, open-label RCT comparing ciltacabtagene autoleucel versus treatment with daratumumab in combination with pomalidomide and dexamethasone (DPd) or pomalidomide in combination with bortezomib and dexamethasone (PVd). The study included adult patients with relapsed and refractory multiple myeloma with 1 to 3 prior therapies and an Eastern Cooperative Oncology Group-Performance Status (ECOG PS) of 0 or 1. Patients had to have been treated with an immunomodulator and a proteasome inhibitor as part of their previous therapies and have a disease refractory to lenalidomide. In addition, patients had to have experienced disease progression according to the International Myeloma Working Group (IMWG) criteria during or within 6 months of their last therapy.

A total of 419 patients were included in the study and randomly allocated in a 1:1 ratio to either treatment with ciltacabtagene autoleucel (N = 208) or a comparator therapy selected from DPd or PVd (N = 211, of which DPd [n = 183] and PVd [n = 28]).

Treatment with ciltacabtagene autoleucel was largely in compliance with the specifications of the Summary of Product Characteristics (SPC). Leukapheresis was performed within 3 to 6 days of randomization. Lymphodepleting chemotherapy was given over 3 days and was to be initiated between Days 5 to 7 before the infusion of ciltacabtagene autoleucel. In the time between leukapheresis and lymphodepleting chemotherapy, all patients were to receive bridging therapy for disease control. This consisted of at least 1 cycle of DPd or PVd. According to the SPC for ciltacabtagene autoleucel, a bridging therapy of physician's choice should be considered in order to reduce the tumour burden or stabilize the disease, and is therefore not absolutely necessary for all patients, which is in contrast to the approach in the CARTITUDE-4 study. Against this background, it is unclear whether bridging therapy was indicated for all patients in the CARTITUDE-4 study. In the control arm, treatment with DPd or PVd had to be initiated on Day 7 after randomization at the latest and was largely carried out in accordance with the corresponding SPC. The choice of the bridging therapy in the intervention arm and the comparator therapy in the control arm was made at the investigator's discretion before randomization, taking into account the previous myeloma therapies.

Primary outcome of the CARTITUDE-4 study was progression-free survival (PFS). Patient-relevant secondary outcomes were outcomes in the categories of mortality, morbidity, health-related quality of life, and side effects.

Implementation of the ACT in the CARTITUDE-4 study

The G-BA defined individualized treatment with a choice of several drug therapy options including autologous or allogeneic stem cell transplantation as ACT. According to the G-BA, the therapy was to be chosen under consideration of the general condition, the drugs and drug combinations used in the prior therapies as well as the type and duration of response to the prior therapies and the eligibility for stem cell transplantation (see Table 2). For the implementation of individualized treatment in a study of direct comparison, it is also expected that the investigators will have a choice of several treatment options (multi-comparator study).

In Module 4 A of the dossier, the company presents extensive information on the pretreatment of the patients included in the study as well as information on the pretreatment of the patients in the control arm, depending on the comparator therapy selected in the study, in order to demonstrate the suitability of the therapies used in the study for the patients in the control arm. From this information, it can be derived that the treatment options administered in the control arm of the study based on the previous therapies (active substances, type and duration of response) were suitable for the patients included. However, the data only partially provide information on the specific drug combinations with which the patients were pretreated, and it remains unclear to what extent other factors listed in the S3 guideline (such as comorbidities) were taken into account when choosing the treatment option. Based on the available data, it can therefore not be ruled out with sufficient certainty that other treatment options mentioned by the G-BA, including in particular daratumumab in combination with carfilzomib and dexamethasone (DKd), isatuximab in combination with carfilzomib and dexamethasone (IsaKd) or elotuzumab in combination with pomalidomide and dexamethasone (EPd), may also have been suitable options, or potentially even more suitable options, for the included patients. Moreover, the CARTITUDE-4 study with 2 out of more than 15 possible treatment options within the framework of an individualized treatment does not reflect the heterogeneity of the treatment landscape in this therapeutic indication.

Overall, it is assumed that the 2 available treatment options in the comparator arm enabled sufficient individualized treatment in the sense of the ACT. However, it is unclear whether other treatment options included in the G-BA's ACT would also have been suitable or even more suitable. This uncertainty is taken into account in the assessment of the certainty of results. Based on the results of the CARTITUDE-4 study, conclusions on the added benefit of ciltacabtagene autoleucel can only be made for those patients for whom treatment with DPd or PVd is the appropriate individualized treatment. Furthermore, based on the results of the

CARTITUDE-4 study, no conclusions can be drawn for patients with at least 4 prior therapies, as only patients with 1 to 3 prior therapies were included in the study.

Use of bridging therapies in the CARTITUDE-4 study

As described above, all patients in the intervention arm of the CARTITUDE-4 study received a bridging therapy, contrary to the specifications of the SPC for ciltacabtagene autoleucel. However, it is not clear from the information in the dossier to what extent bridging therapy was indicated for all patients in the intervention arm. This uncertainty was taken into account in the assessment of the certainty of conclusions of the CARTITUDE-4 study results.

Risk of bias and assessment of the certainty of conclusions

The risk of bias across outcomes is assessed as low for the CARTITUDE-4 study as well as for the results on overall survival. The risk of bias for the results on severe AEs was considered to be high. This is because the reasons that lead to a discontinuation of observation are potentially informative for the occurrence or observation of severe AEs. The risk of bias for the results on discontinuation due to AEs is rated as high due to the subjective decision to discontinue in an unblinded study design.

As described above, there are uncertainties irrespective of the risk of bias, so that it cannot be assumed that the comparator therapies used in the CARTITUDE-4 study represent a complete implementation of the ACT. Moreover, it is unclear whether bridging therapy was indicated for all patients in the CARTITUDE-4 study. It therefore remains unclear whether the results of the study can be transferred without restriction to the German health care context, especially as there are clearly more treatment options available in health care and other patient-specific factors are taken into account in the treatment decision. Thus, at most hints, e.g. of an added benefit, can be derived for all outcomes irrespective of the outcome-specific risk of bias.

Due to fundamental deficiencies and uncertainties in the recording and analysis of patient-reported outcomes and AEs in the CARTITUDE-4 study, the results on outcomes in the categories of morbidity, health-related quality of life and side effects (apart from severe AEs and discontinuation due to AEs) are not suitable for the present assessment. For the patient-reported outcomes, this is mainly due to the fact that relevant periods of the chimeric antigen receptor (CAR) T cell therapy are not taken into account in the recordings and a fair comparison of the treatment concepts in the two treatment arms is therefore impossible. For outcomes in the side effects category, this is mainly due to the fact that certain events were selectively recorded for each patient during the follow-up observation and these phases were taken into account in the analyses.

Results

Mortality

Overall survival

A statistically significant difference in favour of ciltacabtagene autoleucel was shown for the outcome of overall survival. There is a hint of added benefit of ciltacabtagene autoleucel in comparison with individualized treatment selecting from DPd or PVd.

Morbidity

Symptoms (recorded using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 [EORTC QLQ-C30] or Patient Global Impression of Severity [PGIS]), health status (recorded using the EQ-5D Visual Analogue Scale [VAS])

No suitable data are available for symptoms (recorded using EORTC QLQ-C30 and PGIS) and health status (recorded using the EQ-5D VAS). In each case, there is no hint of added benefit of ciltacabtagene autoleucel in comparison with individualized treatment selecting from DPd or PVd; an added benefit is therefore not proven.

Health-related quality of life (recorded using EORTC QLQ-C30)

No suitable data are available for health-related quality of life (recorded using EORTC QLQ-C30). There is no hint of added benefit of ciltacabtagene autoleucel in comparison with individualized treatment selecting from DPd or PVd; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs)

No suitable data were available for the outcome of SAEs. There is no hint of greater or lesser harm from ciltacabtagene autoleucel in comparison with individualized treatment selecting from DPd or PVd; greater or lesser harm is therefore not proven for this outcome.

Severe AEs and discontinuation due to AEs

There was no statistically significant difference between treatment groups for either of the outcomes of severe AEs or discontinuation due to AEs. In each case, there is no hint of greater or lesser harm from ciltacabtagene autoleucel in comparison with individualized treatment selecting from DPd or PVd; greater or lesser harm is therefore not proven for these outcomes.

Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (CTCAE) (PRO-CTCAE)

No suitable data are available for the outcome of PRO-CTCAE. There is no hint of greater or lesser harm from ciltacabtagene autoleucel in comparison with individualized treatment selecting from DPd or PVd; greater or lesser harm is therefore not proven for this outcome.

Cytokine release syndrome, severe neurological toxicity, infusion related reactions, severe infections and secondary malignancies

No suitable data are available for each of the outcomes of cytokine release syndrome, severe neurological toxicity, infusion related reactions, severe infections and secondary malignancies. In each case, there is no hint of greater or lesser harm from ciltacabtagene autoleucel in comparison with individualized treatment selecting from DPd or PVd; greater or lesser harm is therefore not proven for these outcomes.

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 ciltacabtagene autoleucel in comparison with the ACT is assessed as follows:

The overall picture shows a hint of an added benefit with the extent "considerable" for overall survival. The analyses available on the outcomes of the categories of morbidity, health-related quality of life and side effects are largely unsuitable for the present benefit assessment. The only exceptions to this are the analyses on the outcomes of severe AEs and discontinuation due to AEs. However, no disadvantages are expected to an extent that would completely challenge the positive effect in overall survival. However, the extent of the added benefit cannot be quantified due to the lack of data on other outcomes.

In summary, there is a hint of a non-quantifiable added benefit of ciltacabtagene autoleucel over the ACT for adult patients with relapsed and refractory multiple myeloma who have previously received 1 to 3 prior therapies, including 1 immunomodulator and 1 proteasome inhibitor, and who showed disease progression during the last therapy and are refractory to lenalidomide, and for whom DPd or PVd is an appropriate individualized treatment.

For adult patients with relapsed and refractory multiple myeloma who have previously received 1 to 3 prior therapies, including 1 immunomodulator and 1 proteasome inhibitor, and who showed disease progression during the last therapy and are refractory to lenalidomide, and for whom DPd or PVd is not a suitable individualized treatment and for patients who have already received at least 4 prior therapies, no data are available from the CARTITUDE-4 study for the assessment of the added benefit of ciltacabtagene autoleucel

[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].

compared with the ACT. An added benefit of ciltacabtagene autoleucel over the ACT is therefore not proven for patients with 1 to 3 prior therapies for whom DPd or PVd is not a suitable individualized treatment, and for patients with at least 4 prior therapies.

Table 3 shows a summary of probability and extent of the added benefit of ciltacabtagene autoleucel.

Table 3: Ciltacabtagene autoleucel – probability and extent of added benefit (multipage table)

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adults with relapsed and refractory multiple myeloma, who have received at least one prior therapy, including 1 immunomodulator and 1 proteasome inhibitor, who have demonstrated disease progression on the last therapy, and who are refractory to lenalidomide	Individualized treatment[b, c] choosing from ▪ daratumumab in combination with bortezomib and dexamethasone ▪ daratumumab in combination with carfilzomib and dexamethasone ▪ daratumumab in combination with pomalidomide and dexamethasone ▪ isatuximab in combination with carfilzomib and dexamethasone ▪ isatuximab in combination with pomalidomide and dexamethasone[d] ▪ elotuzumab in combination with pomalidomide and dexamethasone[d] ▪ pomalidomide in combination with bortezomib and dexamethasone[e] ▪ pomalidomide in combination with dexamethasone[f, g] ▪ carfilzomib in combination with dexamethasone ▪ panobinostat in combination with bortezomib and dexamethasone[f] ▪ bortezomib in combination with pegylated liposomal doxorubicin[f, g] ▪ bortezomib in combination with dexamethasone[f, g] ▪ daratumumab monotherapy[f, h] ▪ cyclophosphamide as monotherapy or in combination with dexamethasone[f, h] ▪ melphalan as monotherapy or in combination with prednisolone or prednisone[f, h] ▪ high-dose therapy with autologous stem cell transplantation[i] ▪ high-dose therapy with allogeneic stem cell transplantation[j, k] ▪ taking into account the general condition, the drugs and drug combinations used in the prior therapies as well as the type and duration of response to the respective prior therapies and the eligibility for stem cell transplantation[l, m]	▪ Patients with 1 to 3 prior therapies for whom DPd or PVd is a suitable individualized treatment: hint of a non-quantifiable added benefito ▪ Patients with 1 to 3 prior therapies for whom DPd or PVd is not a suitable individualized treatment, and patients with ≥ 4 prior therapies: added benefit not proven

Table 3: Ciltacabtagene autoleucel – probability and extent of added benefit (multipage table)

Therapeutic indication	ACT[a]	Probability and extent of added benefit
a. Presented is the ACT specified by the G-BA. b. For the implementation of individualized treatment in a study of direct comparison, the investigators are expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons). c. According to the G-BA, the duration of response to the prior therapy is a criterion for the individualized treatment. In this respect, according to the generally recognized state of medical knowledge, unsuitability of retreatment with the drugs or drug combinations of the prior therapy is defined as disease progression under the respective prior therapy or a duration of response of less than 12 months after completion of the respective prior therapy. Accordingly, for patients with relapsed disease who show a response in the form of CR, VGPR and PR of more than 12 months after completion of the prior therapy, treatment using the drugs or drug combinations used in the prior therapy may also be a suitable treatment option. d. Only for patients with at least 2 prior therapies. e. Only for patients who are refractory to a CD38 antibody. f. Only for patients who have received at least 4 prior therapies. g. Only for at least double-refractory patients for whom triplet therapy is not suitable. h. Only for at least triple-refractory patients for whom triplet or doublet therapy is not suitable. i. Only for patients after 1 prior therapy for whom autologous stem cell transplantation is an option; after achieving remission. Autologous stem cell transplantation should be offered to all patients eligible for transplantation who have not undergone transplantation as part of first-line therapy. In addition, an autologous re-transplantation can be performed if the progression-free survival after the first transplantation generally lasted at least 18 months. j. Only for patients after 1 prior therapy for whom allogeneic stem cell transplantation is an option; after achieving remission. Allogeneic stem cell transplantation is a treatment option for patients with primary refractoriness and an early relapse after autologous stem cell transplantation. k. The requirements of the "G-BA guideline on the testing of allogeneic stem cell transplantation in multiple myeloma beyond first-line therapy", the "G-BA's decision on measures of quality assurance for allogeneic stem cell transplantation in multiple myeloma (QS-B SZT MM)" and §137c of the German Social Code Book V shall apply with regard to the use of allogeneic stem cell transplantation. l. According to the G-BA, unsuitability of triplet or doublet therapy should be justified based on refractoriness and comorbidity of the patients and taking into account the toxicity of the respective therapy. m. According to the G-BA, patients in the present therapeutic indication are assumed to generally continue antineoplastic treatment. Best supportive care is therefore not considered an ACT. o. The CARTITUDE-4 study included only patients with an ECOG PS of 0 or 1. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2. DPd: daratumumab in combination with pomalidomide and dexamethasone; ECOG-PS: Eastern Cooperative Oncology Group – Performance Status; G-BA: Federal Joint Committee; CD: cluster of differentiation; CR: complete response; PR: partial response; PVd: pomalidomide in combination with bortezomib and dexamethasone; SGB: Social Code Book; VGPR: very good partial response		

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

Supplementary note

The result of the assessment deviates from the result of the G-BA's assessment conducted in the context of the market launch in 2023. There, the G-BA had determined a non-quantifiable added benefit of ciltacabtagene autoleucel for patients with at least 3 prior therapies according to the first approval. However, in said assessment, the added benefit had been regarded as proven by the approval irrespective of the underlying data because of the special situation for orphan drugs.

I 2 Research question

The aim of the present report is to assess the added benefit of ciltacabtagene autoleucel compared with an individualized treatment as ACT in adult patients with relapsed and refractory multiple myeloma who have previously received at least 1 therapy, including 1 immunomodulator and 1 proteasome inhibitor, and who have experienced disease progression during the last therapy and are refractory to lenalidomide.

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of ciltacabtagene autoleucel (multipage table)

Therapeutic indication	**ACT**[a]
Adults with relapsed and refractory multiple myeloma, who have received at least one prior therapy, including 1 immunomodulator and 1 proteasome inhibitor, who have demonstrated disease progression on the last therapy, and who are refractory to lenalidomide	Individualized treatment[b, c] choosing from ▪ daratumumab in combination with bortezomib and dexamethasone ▪ daratumumab in combination with carfilzomib and dexamethasone ▪ daratumumab in combination with pomalidomide and dexamethasone ▪ isatuximab in combination with carfilzomib and dexamethasone ▪ isatuximab in combination with pomalidomide and dexamethasone[d] ▪ elotuzumab in combination with pomalidomide and dexamethasone[d] ▪ pomalidomide in combination with bortezomib and dexamethasone[e] ▪ pomalidomide in combination with dexamethasone[f, g] ▪ carfilzomib in combination with dexamethasone ▪ panobinostat in combination with bortezomib and dexamethasone[f] ▪ bortezomib in combination with pegylated liposomal doxorubicin[f, g] ▪ bortezomib in combination with dexamethasone[f, g] ▪ daratumumab monotherapy[f, h] ▪ cyclophosphamide as monotherapy or in combination with dexamethasone[f, h] ▪ melphalan as monotherapy or in combination with prednisolone or prednisone[f, h] ▪ high-dose therapy with autologous stem cell transplantation[i] ▪ high-dose therapy with allogeneic stem cell transplantation[j, k] ▪ taking into account the general condition, the drugs and drug combinations used in the prior therapies as well as the type and duration of response to the respective prior therapies and the eligibility for stem cell transplantation[l, m]

Table 4: Research question for the benefit assessment of ciltacabtagene autoleucel (multipage table)

Therapeutic indication	ACT[a]
a. Presented is the ACT specified by the G-BA. b. For the implementation of individualized treatment in a study of direct comparison, the investigators are expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons). c. According to the G-BA, the duration of response to the prior therapy is a criterion for the individualized treatment. In this respect, according to the generally recognized state of medical knowledge, unsuitability of retreatment with the drugs or drug combinations of the prior therapy is defined as disease progression under the respective prior therapy or a duration of response of less than 12 months after completion of the respective prior therapy. Accordingly, for patients with relapsed disease who show a response in the form of CR, VGPR and PR of more than 12 months after completion of the prior therapy, treatment using the drugs or drug combinations used in the prior therapy may also be a suitable treatment option. d. Only for patients with at least 2 prior therapies. e. Only for patients who are refractory to a CD38 antibody. f. Only for patients who have received at least 4 prior therapies. g. Only for at least double-refractory patients for whom triplet therapy is not suitable. h. Only for at least triple-refractory patients for whom triplet or doublet therapy is not suitable. i. Only for patients after 1 prior therapy for whom autologous stem cell transplantation is an option; after achieving remission. Autologous stem cell transplantation should be offered to all patients eligible for transplantation who have not undergone transplantation as part of first-line therapy. In addition, an autologous re-transplantation can be performed if the progression-free survival after the first transplantation generally lasted at least 18 months. j. Only for patients after 1 prior therapy for whom allogeneic stem cell transplantation is an option; after achieving remission. Allogeneic stem cell transplantation is a treatment option for patients with primary refractoriness and an early relapse after autologous stem cell transplantation. k. The requirements of the "G-BA guideline on the testing of allogeneic stem cell transplantation in multiple myeloma beyond first-line therapy" Gemeinsamer Bundesausschuss, 2017 #26}, the "G-BA's decision on measures of quality assurance for allogeneic stem cell transplantation in multiple myeloma (QS-B SZT MM)" [3] and §137c of the German Social Code Book V shall apply with regard to the use of allogeneic stem cell transplantation. l. According to the G-BA, unsuitability of triplet or doublet therapy should be justified based on refractoriness and comorbidity of the patients and taking into account the toxicity of the respective therapy. m. According to the G-BA, patients in the present therapeutic indication are assumed to generally continue antineoplastic treatment. Best supportive care is therefore not considered an ACT.	

CD: cluster of differentiation; CR: complete response; G-BA: Federal Joint Committee; PR: partial response; SGB: Social Code Book; VGPR: very good partial response

The G-BA adjusted the ACT after submission of the dossier on 7 January 2025, as shown in Table 4. In its dossier, the company uses the ACT from the procedure on idecabtagene vicleucel to derive the ACT [4]. The resulting definition of the comparator therapy by the company largely corresponds to the current ACT of the G-BA of 7 January 2025. In deviation from this, however, the company does not name high-dose therapy followed by autologous stem cell transplantation and high-dose therapy followed by allogeneic stem cell

transplantation as treatment options within the framework of individualized treatment. However, this deviation has no consequences for the benefit assessment, as it has no impact on the completeness of the study pool. The present assessment is conducted on the basis of the ACT specified by the G-BA.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs are used to derive the added benefit. This concurs with the company's inclusion criteria.

I 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 ciltacabtagene autoleucel (status: 23 October 2024)
- bibliographical literature search on ciltacabtagene autoleucel (last search on 2 September 2024)
- search in trial registries/trial results databases for studies on ciltacabtagene autoleucel (last search on 7 November 2024)
- search on the G-BA website for ciltacabtagene autoleucel (last search on 11 October 2024)

To check the completeness of the study pool:

- search in trial registries for studies on ciltacabtagene autoleucel (last search on 12 December 2024); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

I 3.1 Studies included

The study presented in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: ciltacabtagene autoleucel vs. individualized treatment

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
Study 68284528MMY3002 (CARTITUDE-4[d])	Yes	Yes	No	Yes [5-8]	Yes [9-11]	Yes [12-14]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to by this acronym.

DPd: Daratumumab in combination with pomalidomide and dexamethasone; G-BA: Federal Joint Committee; PVd: pomalidomide in combination with bortezomib and dexamethasone; RCT: randomized controlled trial

The study pool of the present benefit assessment comprises the RCT CARTITUDE-4. This corresponds to the study pool of the company.

I 3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the included study – RCT, direct comparison: ciltacabtagene autoleucel versus individualized treatment, selecting from DPd or PVd (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
CARTITUDE-4	RCT, open-label, parallel	Patients (≥ 18 years) with relapsed and refractory multiple myeloma ▪ 1-3 prior therapies[b], including 1 immunomodulator and 1 proteasome inhibitor ▪ refractory diseasec to lenalidomide according to IMWG criteria ▪ disease progression according to IMWG criteria within 6 months of the last therapy[d] ▪ ECOG PS ≤ 1	Ciltacabtagene autoleucel (N = 208) comparator therapy at the investigator's discretion[e] (N = 211) ▪ daratumumab + pomalidomide + dexamethasone (DPd, n = 183) ▪ pomalidomide + bortezomib + dexamethasone (PVd, n = 28)	Screening: ≤ 28 days before randomization treatment: ▪ ciltacabtagene autoleucel: single infusion; preceded by leukapheresis followed by bridging therapy[e] and lymphocyte depletion ▪ comparator therapies: until disease progression, unacceptable toxicity or withdrawal of consent observation[f]: outcome-specific, at most until withdrawal of consent or end of study[g]	81 centres in Australia, Belgium, Denmark, France, Germany, Greece, Israel, Italy, Japan, Netherlands, Poland, Sweden, South Korea, Spain, United Kingdom, USA 06/2020–ongoing data cut-offs: ▪ 1 November 2022h ▪ 17 April 2023[i] ▪ 13 December 2023j ▪ 1 May 2024[k]	Primary: PFS secondary: overall survival, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the included study – RCT, direct comparison: ciltacabtagene autoleucel versus individualized treatment, selecting from DPd or PVd (multipage table)

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

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. Induction therapy with or without subsequent stem cell transplantation, consolidation and maintenance therapy was counted as 1 prior therapy.
c. Refractory disease was defined as failure to achieve a minimal response or as progression during or within 60 days of completion of lenalidomide therapy; in patients with more than 1 prior therapy, refractory disease could also have occurred in an earlier line of treatment than the last.
d. In patients with only 1 prior therapy, disease progression had to have occurred within 36 months of a stem cell transplantation, otherwise within 42 months of the start of first-line therapy.
e. Taking into account the patient's previous treatment regimen.
f. Outcome-specific information is provided in Table 9.
g. According to the study design after the occurrence of approximately 250 death events.
h. Prespecified 1st interim analysis for PFS and overall survival, planned after approx. 188 PFS events (approx. 75% of expected PFS events).
i. Analysis prepared for the FDA as part of the 120-day safety update.
j. Data cut-off on overall survival required by the EMA as part of the European approval procedure.
k. Final prespecified analysis for PFS and prespecified 2nd interim analysis for overall survival, after approximately 250 PFS events. A further 3rd prespecified interim analysis for overall survival is planned at approximately 200 death events, and the final analysis at approximately 250 death events.

AE: adverse event; DPd: daratumumab in combination with pomalidomide and dexamethasone; ECOG PS: Eastern Cooperative Oncology Group - Performance Status; EMA: European Medicines Agency; FDA: Food and Drug Administration; IMWG: International Myeloma Working Group; n: subpopulation; N: number of randomized patients; PFS: progression-free survival; PVd: pomalidomide in combination with bortezomib and dexamethasone; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd (multipage table)

Study	Intervention	Comparison[a]
CARTITUDE-4	Ciltacabtagene autoleucel: single IV administration of 0.5-1 × 10^6 CAR-positive viable T-cells/kg[b] <u>necessary preparations:</u> ▪ leukapheresis (3-6 days after randomization) to obtain PBMCs for the production of ciltacabtagene autoleucel ▪ bridging therapya for disease control between leukapheresis and before the start of lymphocyte depletion (start ≤ 7 days after randomization) ▫ ≥ 1 cycle[c] consisting of the combinations DPd or PVd administered as in the control arm ▪ lymphodepleting chemotherapy (initiation 5-7 days before administration of ciltacabtagene autoleucel)[d]: ▫ fludarabine IV 30 mg/m² BSA/day for 3 days ▫ cyclophosphamide IV 300 mg/m² BSA/day for 3 days ▪ premedication before ciltacabtagene autoleucel infusion: ▫ paracetamol 650-1000 mg orally or IV ▫ diphenhydramine 50 mg orally or IV (or equivalent)	DPd (cycle length 28 days): ▪ daratumumab 1800 mg, SC ▫ cycles 1-2 on Days 1, 8, 15, 22 ▫ cycles 3-6 on Days 1 and 15 ▫ from cycle 7 on Day 1 ▪ pomalidomide 4 mg orally on Days 1 to 21 ▪ dexamethasone 40 mg (or 20 mg if > 75 years or ≤ 75 years and BMI < 18.5 kg/m²) orally or intravenously on Days 1, 8, 15 and 22[e] ▪ premedication before infusion of daratumumab: ▫ paracetamol 650-1000 mg orally or IV ▫ diphenhydramine 25-50 mg orally or IV (or equivalent) ▫ leukotriene inhibitor 10 mg orally (optional on Day 1 of cycle 1) or PVd (cycle length 21 days): ▪ pomalidomide 4 mg orally on Days 1 to 14 ▪ bortezomib 1.3 mg/m² BSA SC ▫ cycles 1-8 on Days 1, 4, 8 and 11 ▫ from cycle 9 on Days 1 and 8 ▪ dexamethasone 20 mg (or 10 mg if > 75 years) orally ▫ cycles 1-8 on Days 1, 2, 4, 5, 8, 9, 11 and 12 ▫ from Cycle 9 on Days 1, 2, 8 and 9
	Dose adjustment: ▪ lymphodepleting chemotherapy: ▫ fludarabine: 24 mg/m² BSA/day at an eGFR of 30-70 mL/min/1.73m²	▪ Dose adjustments according to the respective country-specific SPC and at the investigator's discretion ▪ if one component of the study medication is interrupted or permanently discontinued, treatment can be continued with the remaining components.
	Required pretreatment ▪ 1-3 therapy lines, including 1 immunomodulator and 1 proteasome inhibitor	

Table 7: Characteristics of the intervention – RCT, direct comparison: ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd (multipage table)

Study	Intervention	Comparison[a]
CARTITUDE-4	**Non-permitted pretreatment** ▪ therapies with BCMA as target structure ▪ any CAR T cell therapy ▪ corticosteroids with a cumulative dose of ≥ 70 mg prednisone within 7 days prior to randomization ▪ monoclonal antibodies within 21 days prior to randomization ▪ targeted therapy, epigenetic or experimental therapy within 14 days or at least 5 half-lives before randomization, whichever is shorter ▪ cytotoxic therapy, proteasome inhibitors or radiotherapyf within 14 days prior to randomization ▪ immunomodulators within 7 days prior to randomization ▪ autologous stem cell transplantation within 12 weeks and allogeneic stem cell transplantation within 6 months prior to apheresis	
	permitted concomitant treatment ▪ supportive standard therapies (e.g. antiemetics, antidiarrhoeals and other therapies to treat symptoms/signs of the disease) and therapies to treat CAR T cell therapy-specific toxicity (e.g. cytokine release syndrome) ▪ bisphosphonates ▪ (oral or intravenous) antibiotics or other anti-infectives for the treatment of infections ▪ haematopoietic growth factors and platelet and erythrocyte transfusions	
	non-permitted concomitant treatment ▪ other chemotherapies, anti-cancer-immunotherapies or experimental therapies ▪ other immunosuppressants ▪ orthopaedic surgeries or radiotherapy[g] ▪ for patients being treated with ciltacabtagene autoleucel ▪ corticosteroids between lymphodepleting chemotherapy and Day 112 after infusion of ciltacabtagene autoleucel except for the treatment of cytokine release syndrome and severe neurotoxicity ▫ RANK ligand inhibitors (e.g. denosumab) ▫ pegylated myeloid growth factors (e.g. pegfilgrastim) within 112 days after infusion of ciltacabtagene autoleucel	

Table 7: Characteristics of the intervention – RCT, direct comparison: ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd (multipage table)

Study	Intervention	Comparison[a]

a. At the investigator's discretion, taking into account the patients' previous treatment regimen.
b. The target dose was 0.75×10^6 per kg of body weight and the maximum dose was 1×10^8 CAR-positive viable T cells.
c. Depending on the clinical condition of the patient and the availability of ciltacabtagene autoleucel, several cycles of bridging therapy could be administered. After Cycle 1, the cycles within the bridging therapy can also be discontinued prematurely in order to ensure an adequate washout phase before the start of lymphodepleting chemotherapy.
d. Before the initiation of lymphodepleting chemotherapy, the following washout phases had to be observed for the bridging therapy: daratumumab 21 days, bortezomib 14 days, pomalidomide and dexamethasone 7 days.
e. The total dose could be distributed to 2 consecutive days as of Cycle 1 (in patients < 75 years) or as of Cycle 2 (in patients > 75 years or ≤ 75 years and BMI < 18.5 kg/m^2). On the days of the daratumumab infusion, dexamethasone had to be administered as prophylaxis 1 to 3 hours before the administration of daratumumab; if the infusion was split over 2 days, the second half was administered on the day after the daratumumab administration.
f. Palliative radiation of less than 5% of the bone marrow (except for measurable extramedullary plasmacytomas) was permitted.
g. Were only permitted in the absence of disease progression and after consultation with the sponsor; emergency interventions were also possible without consultation with the sponsor

BCMA: B-cell maturation antigen; BMI: body mass index; BSA: body surface area; CAR: chimeric antigen receptor; CTCAE: Common Terminology Criteria for Adverse Events; DPd: daratumumab in combination with pomalidomide and dexamethasone; eGFR: estimated glomerular filtration rate; IV: intravenous; PBMC: peripheral blood mononuclear cells; PVd: pomalidomide in combination with bortezomib and dexamethasone; RANK: receptor activator of NF-κB; RCT: randomized controlled trial; SC: subcutaneous

Study design

The CARTITUDE-4 study is an ongoing, open-label RCT comparing ciltacabtagene autoleucel versus treatment with DPd or PVd. The study included adult patients with relapsed and refractory multiple myeloma with 1 to 3 prior therapies and an ECOG PS of 0 or 1. Induction therapy with or without subsequent stem cell transplantation, consolidation and maintenance therapy was considered as one prior treatment. Patients had to have been treated with an immunomodulator and a proteasome inhibitor as part of their previous therapies and have a disease refractory to lenalidomide. In addition, patients had to have experienced disease progression according to the IMWG criteria during or within 6 months of their last therapy.

A total of 419 patients were included in the study and randomly allocated in a 1:1 ratio to either treatment with ciltacabtagene autoleucel (N = 208) or a comparator therapy selected from DPd or PVd (N = 211, of which DPd [n = 183] and PVd [n = 28]). Randomization was stratified by treatment choice (DPd vs. PVd), by International Staging System (ISS) stage (I vs. II vs. III) and by number of previous myeloma therapies (1 vs. 2 or 3).

Treatment with ciltacabtagene autoleucel was largely in compliance with the specifications of the SPC [15]. Leukapheresis was performed within 3 to 6 days of randomization. Lymphodepleting chemotherapy was given over 3 days and was to be initiated between Days 5 to 7 before the infusion of ciltacabtagene autoleucel. In the CARTITUDE-4 study, patients received 0.5 to 1 × 10^6 CAR-positive viable T cells once.

In the period between leukapharesis and lymphodepleting chemotherapy, all patients were to be receive a bridging therapy for disease control, which should begin on Day 7 after randomization at the latest. The bridging therapy consisted of at least 1 cycle of DPd or PVd. The drug combination was selected prior to randomization taking into account previous myeloma therapies and thus also corresponded to the therapy that the patients would have received if they had been allocated to the control arm. Between the bridging therapy and the start of lymphodepleting chemotherapy, wash-out times had to be observed depending on the drug used. These were at least 21 days for daratumumab, 14 days for bortezomib and 7 days for pomalidomide or dexamethasone. Patients who experienced disease progression during the bridging therapy could continue to receive ciltacabtagene autoleucel within the framework of the study. However, according to the study design, this was categorized as subsequent therapy. For the present assessment, however, it is assumed that in the intervention arm, treatment with ciltacabtagene autoleucel is also carried out in the event of disease progression under the bridging therapy as part of the current line of treatment, and therefore does not represent a subsequent therapy.

According to the SPC for ciltacabtagene autoleucel [15], a bridging therapy of physician's choice should be considered in order to reduce the tumour burden or stabilize the disease, and is therefore not absolutely necessary for all patients, which is in contrast to the approach in the CARTITUDE-4 study. In light of the recommendation in the SPC, it is unclear whether bridging therapy was indicated for all patients in the CARTITUDE-4 study (see "Use of bridging therapy" in the CARTITUDE-4 study).

In the control arm, treatment with DPd or PVd had to start on Day 7 after randomization at the latest and was, as far as possible, carried out in accordance with the corresponding SPC [16-19]. The therapy was chosen at the investigator's discretion before randomization, taking into account the previous myeloma therapies. Patients in the control arm did not have the option of receiving ciltacabtagene autoleucel as a subsequent therapy as part of the study.

Patients who received ciltacabtagene autoleucel in the CARTITUDE-4 study will continue to be observed for overall survival and side effects in the long-term follow-up study 68284528MMY4002 [20] after completion of the study.

Primary outcome of the CARTITUDE-4 study is PFS. Patient-relevant secondary outcomes comprise outcomes in the categories of mortality, morbidity, health-related quality of life and side effects.

Implementation of the ACT in the KEYNOTE 4 study

The G-BA specified individualized treatment as ACT, taking into account the general condition, the drugs and drug combinations used in the prior therapies as well as the type and duration of response to the prior therapies and the eligibility for stem cell transplantation. Depending on the number of previous therapies and refractoriness, various options can be considered as part of an individualized treatment, including triple and dual combinations from the drug classes of monoclonal antibodies, immunomodulators and proteasome inhibitors, each combined with dexamethasone, daratumumab as monotherapy and classic chemotherapeutic agents as combination or monotherapy. In addition, according to the G-BA, high-dose therapy followed by autologous or allogeneic stem cell transplantation may also be considered as treatment options for patients with 1 prior therapy under certain circumstances (see Table 4). In its notes on the ACT, the G-BA additionally points out that for implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options, according to the G-BA.

According to the S3 guideline "*Diagnosis, treatment and follow-up of patients with monoclonal gammopathy of undetermined significance (MGUS) or multiple myeloma*" [21] valid at the time of this assessment, the choice of relapse therapy depends not only on previous therapies but also on other patient-specific factors, such as refractory status, general condition, comorbidities, tolerability and duration of response in previous lines of treatment. Therefore, all drug classes are usually used and combined in an individual sequence. Nevertheless, the S3 guideline makes a strong recommendation for patients who received 1 to 3 prior therapies of a triple combination therapy with two different substances from the drug classes of monoclonal antibodies, immunomodulator, proteasome inhibitor and a steroid, taking into account the increased toxicity. In addition to drug therapies, stem cell transplantation is also a possible treatment option according to the S3 guideline. Autologous stem cell transplantation should therefore be offered to all patients who are eligible for transplantation and who have not undergone transplantation as part of the first-line treatment. In contrast, autologous re-transplantation can be performed if the PFS after the first transplantation has generally lasted at least 18 months. Patients with early relapse after autologous stem cell transplantation can also be offered an allogeneic stem cell transplantation.

In the control arm of the CARTITUDE-4 study, DPd or PVd were the only available treatment options. Although these treatment options are covered by the G-BA's ACT, the CARTITUDE-4

study only offered a significantly limited selection of the treatment options comprised in the ACT. In accordance with the study protocol, the choice of the treatment option in the CARTITUDE study-4 was made in consideration of the prior therapies. In Module 4 A of the dossier, the company presents extensive information on the pretreatment of the patients included in the study as well as information on the pretreatment of the patients in the control arm, depending on the comparator therapy selected in the study, in order to demonstrate the suitability of the therapies used in the study for the patients in the control arm.

Data available for the control arm on the pre-treatment of patients depending on the comparator therapy chosen in the study are listed in Table 8 below.

Table 8: Information on pre-treatment in the control arm depending on the treatment option administered in the CARTITUDE-4 study

Study characteristic category	DPd N[a] = 183	PVd N[a] = 28
CARTITUDE-4		
Number of prior therapies, n (%)		
1	67 (36.6)	1 (3.6)
2	74 (40.4)	13 (46.4)
3	42 (23.0)	14 (50.0)
Refractory to, n (%)		
Immunomodulator	183 (100)	28 (100)
Proteasome inhibitor	80 (43.7)	16 (57.1)
Anti-CD38	21 (11.5)	25 (89.3)
Prior therapy includes at least 1 drug of the comparator therapy, n (%)		
No	147 (80.3)	3 (10.7)
Yes	36 (19.7)	25 (89.3)
Daratumumab	27 (14.8[b])	–[c]
Pomalidomide	8 (4.4[b])	0 (0)
Daratumumab and pomalidomide	1 (0.5[b])	–[c]
Bortezomib	–[c]	24 (85.7[b])
Pomalidomide and bortezomib	–[c]	1 (3.6[b])
Response ≥ PR, n (%)	25 (69.4[d])	25 (100[d])
Median duration of prior therapy, [months[e, f]]	11.9	11.0

a. Depending on the column, percentages are calculated with the number of patients in the control arm who received DPd or who received PVd being the denominator. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Institute's calculation related, depending on the column, to the number of patients in the control arm who received DPd or who received PVd.
c. For patients who received DPd in the control arm, the information on prior therapies is provided exclusively for daratumumab and pomalidomide; for patients in the control arm who received PVd, information is provided exclusively for pomalidomide and bortezomib.
d. The number of patients in the control arm who have already received daratumumab and/or pomalidomide (n = 36) or pomalidomide and/or bortezomib (n = 25) in at least 1 prior therapy is used as the denominator for the percentages.
e. If patients have received one of the drugs in more than one prior therapy, the prior therapy with the best response is used for the assessment.
f. The median duration of prior therapy was calculated for patients with a response ≥ PR.

CD: cluster of differentiation; DPd: daratumumab in combination with pomalidomide and dexamethasone; n: number of patients in the category; N: number of randomized patients; PR: partial response; PVd: pomalidomide in combination with bortezomib and dexamethasone

In the control arm of the CARTITUDE study-4, 183 (87%) of the patients received DPd and 28 (13%) received PVd as comparator therapy. In the group that received DPd as comparator therapy, the proportion of patients with refractory disease to a CD38 antibody was significantly lower (around 11%) than in the group that received PVd as comparator therapy (around 89%). Approximately 20% of patients in the DPd group and 89% in the PVd group had already received 1 prior that included at least 1 of the drugs administered in the study. Only a few patients had already been pretreated with the combination of daratumumab and pomalidomide or pomalidomide and bortezomib used in the study. Approximately 69% of patients in the DPd group and all patients in the PVd group who had received prior therapy with at least 1 drug of the respective comparator therapy had at least a partial response to one of these therapies with a median response duration of approximately 12 months.

From the data presented by the company, it can be derived that the treatment options administered in the control arm of the study based on the prior therapies (drugs, type and duration of response) were suitable for the patients included. However, the data only partially provide information on the specific drug combinations with which the patients were pretreated, and it remains unclear to what extent other factors listed in the S3 guideline (such as comorbidities) were taken into account when choosing the treatment option. Based on the available data, it can therefore not be ruled out with sufficient certainty that other treatment options mentioned by the G-BA, including in particular DKd, IsaKd or EPd, may also have been suitable options, or potentially even more suitable options, for the included patients. Moreover, the CARTITUDE-4 study with 2 out of more than 15 possible treatment options within the framework of an individualized treatment does not reflect the heterogeneity of the treatment landscape in this therapeutic indication. With only 2 treatment options, the treating physicians had significantly fewer choices available to them than would be the case in the German health care context. Irrespective of the existing uncertainties, the 2 treatment options that were available in the CARTITUDE-4 study are covered by the G-BA’s ACT and represent relevant treatment options in the present therapeutic indication. Taking into account the information provided by the company in Module 4 A of the dossier on pretreatment and the response of patients in the control arm, it is assumed that the majority of patients included in the CARTITUDE-4 study received sufficient individualized treatment in the sense of the ACT.

Conclusion on the implementation of the ACT

Overall, it is assumed that the 2 available treatment options in the comparator arm enabled sufficient individualized treatment in the sense of the ACT. However, it is unclear whether other treatment options included in the G-BA's ACT would also have been suitable or even more suitable. This uncertainty is taken into account when assessing the certainty of conclusions (see Section I 4.2).

Based on the results of the CARTITUDE-4 study, conclusions on the added benefit of ciltacabtagene autoleucel can only be made for those patients for whom treatment with DPd or PVd is the appropriate individualized treatment. Furthermore, based on the results of the CARTITUDE-4 study, no conclusions can be drawn for patients with at least 4 prior therapies, as only patients with 1 to 3 prior therapies were included in the study.

Use of bridging therapies in the CARTITUDE-4 study

In the CARTITUDE-4 study, all patients in the intervention arm received at least 1 cycle of bridging therapy with DPd or PVd. The choice of DPd or PVd was analogous to the therapy choice in the control arm (see above). According to the SPC [15] for ciltacabtagene autoleucel, bridging therapy should be considered at the discretion of the treating physician in order to reduce the tumour burden or stabilize the disease. However, it is not clear from the information available in the dossier to what extent bridging therapy was indicated for all patients in the intervention arm and whether the treatment was thus in line with the SPC. This uncertainty is taken into account in the assessment of the certainty of conclusions of the results from the CARTITUDE-4 study (see Section I 4.2).

Suitability of the total population of the CARTITUDE-4 study for the benefit assessment

In Module 4 A of the dossier, the company states that 6 patients were included in the CARTITUDE-4 study who showed disease progression more than 60 days after the last therapy and are therefore not included in the therapeutic indication of ciltacabtagene autoleucel, which requires refractory disease. The company further states that 3 patients in the control arm received PVd but did not have disease refractory to a CD38 antibody, although this requirement has to be met according to the ACT specified by the G-BA for treatment with PVd to be a suitable treatment option. As these aspects only affect a small proportion of the patients included (around 1% each), there are no consequences for the present assessment and the total population of the study is used for the benefit assessment. For the outcome "overall survival", the company also presented a sensitivity analysis in Module 4 A of the dossier, in which it did not consider these 9 patients. The result of this analysis is consistent with that of the main analysis and is therefore not considered further below.

Data cut-offs

A total of 4 data cut-offs are available for the CARTITUDE-4 study:

- First data cut-off of 01 November 2022: pre-specified interim analysis triggered by the achievement of 188 events in the primary outcome of PFS
- 2nd data cut-off of 17 April 2023: analysis created as part of the 120-day safety update for the US Food and Drug Administration (FDA)

- 3rd data cut-off of 13 December 2023: data cut-off requested by the European Medicines Agency (EMA) for overall survival
- 4th data cut-off of 01 May 2024: pre-specified interim for the outcome of overall survival triggered by the achievement of 250 events in the outcome of PFS

According to the study planning, a further interim analysis is planned for the outcome of overall survival with approximately 200 death events. According to the study design, the final analysis on the outcome of overall survival and at the same time the end of the study is planned at around 250 death events.

The 4th data cut-off of 1 May 2024 is used for the present benefit assessment. This concurs with the company's approach.

Planned duration of follow-up observation

Table 9 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 9: Planned duration of follow-up observation – RCT, direct comparison: ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd (multipage table)

Study **outcome category** **outcome**	**Planned follow-up observation**	
CARTITUDE-4		
Mortality		
Overall survival	Until death, withdrawal of consent, or end of study[a]	
Morbidity		
Symptoms (EORTC QLQ-C30, PGIS)	Until death, withdrawal of consent, or disease progression	
Health status (EQ-5D VAS)	Until death, withdrawal of consent, or end of study[a]	
Health-related quality of life		
EORTC QLQ-C30	Until death, withdrawal of consent, or disease progression	
Side effects	**Intervention arm**	**Control arm**
AEs and severe AEs[b]	30 days after the last dose of the bridging therapy or until Day 112 after infusion of ciltacabtagene autoleucel, whichever occurs later[c, d]	30 days after the last dose of the comparator therapy or the start of a subsequent therapy, whichever comes first[c, d]
SAEs	Until the end of the study[a, e,]	30 days after the last dose of the comparator therapy or the start of a subsequent therapy, whichever comes first[c, f]
Further outcomes on AEs[g]		
- Secondary malignancies (AEs, SAEs and severe AEs[b])	Until the end of the study[a]	
- Cytokine release syndrome - neurotoxicity - infections (severe AEs[b]) - neurological disorders (AEs, SAEs and severe AEs[b])	Until the end of the study[a, e,]	–[h]
PRO-CTCAE	Until death, withdrawal of consent, or disease progression	

Table 9: Planned duration of follow-up observation – RCT, direct comparison: ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd (multipage table)

Study outcome category outcome	Planned follow-up observation
a. According to the study plan, the study is scheduled to end after the occurrence of approximately 250 death events. b. Operationalized according to CTCAE grade ≥ 3. c. For patients who did not receive any study medication (in addition to ciltacabtagene autoleucel, this also includes leukapheresis, bridging therapy and lymphodepleting chemotherapy): until progression or initiation of subsequent therapy, whichever comes first. d. In addition, AEs suspected to be associated with the study medication will be observed until the end of the study. e. It is not clear from the available data whether these outcomes are to be followed up until the end of the study for all randomized patients in the intervention arm; for an explanation, see the following text section f. Moreover, SAEs suspected to be associated with the study medication will be followed up until the end of the study in the control arm. g. Events labelled as "AEs of special interest" or "delayed AEs" according to the study documents with a planned deviating observation period. h. It is not clear from the available information how these AEs are to be followed up in the control arm. For reasons, see the following section.	
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; DPd: daratumumab in combination with pomalidomide and dexamethasone; EORTC: European Organisation for Research and Treatment of Cancer; PGIS: Patient Global Impression of Severity; PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; PVd: pomalidomide in combination with bortezomib and dexamethasone; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale	

In the CARTITUDE-4 study, follow-up observation until the end of the study is only planned for the outcomes of overall survival, health status (recorded using the EQ-5D VAS) and secondary malignancies in both treatment arms.

For all patient-reported outcomes except health status, the observation periods are systematically shortened in both treatment arms, as they are only recorded until disease progression.

The planned duration of the follow-up observation for of the outcomes in the side effects category in the CARTITUDE-4 study is complex and cannot be clearly determined from the study documents, in part due to discrepant information. The planned follow-up duration already varies between the treatment arms for the superordinate outcomes in the side effects category (see Table 9). The information provided by the company in the dossier also shows that in the course of the study, not all AEs that occurred, but only those with a suspected causal relationship with the study medication as well as individual adverse event (AE) outcomes (referred to by the company as "AEs of special interest" or "delayed AEs",

summarized below as AEs of special interest) were recorded. In addition, the recording of AEs of special interest might also differ between the treatment arms.

It is not clear from the available data whether or when the complete recording of all AEs per patient in the treatment arms will end and which AEs are subsequently subject to further observation. For SAEs and AEs of special interest, it is also unclear whether patients in the intervention arm who did not receive a CAR T cell infusion will also be observed until the end of the study or only until progression or initiation of subsequent therapy, whichever occurs first. For patients who received ciltacabtagene autoleucel after disease progression under the bridging therapy, it also remains unclear to what extent follow-up observation was carried out for outcomes in the side effects category, as the CAR T cell infusion was considered a subsequent therapy for these patients according to the study design. It is also not clear from the study documents whether or for how long AEs of special interest should be followed up in the control arm.

Overall, according to the specified requirements, the differences in the follow-up planning mean that all AEs or SAEs occurring in the individual patients in the CARTITUDE-4 study are fully recorded for different lengths of time depending on the treatment arm and outcome. For the subsequent period, it remains unclear, particularly for the intervention arm, whether only certain events are recorded for the individual patient, i.e. whether events are only recorded if there is a suspected connection with the study medication and/or whether only AEs of special interest are recorded. These uncertainties affect the suitability of the analyses presented on the outcomes in the side effects category (see comments on the analyses on AEs presented by the company in Section I 4.1).

In order to draw a reliable conclusion on the entire study period or the time to patient death, it would be necessary to record all outcomes in both treatment arms over the entire period, as was done for overall survival, health status and secondary malignancies.

Characteristics of the study population

Table 10 shows the patient characteristics of the included study.

Table 10: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd (multipage table)

Study characteristic category	**Ciltacabtagene autoleucel N = 208**	**Individualized treatment choosing from DPd or PVd N = 211**
CARTITUDE-4		
Age [years], mean (SD)	60 (10)	60 (9)
Age group, n (%)		
< 65 years	126 (61)	131 (62)
65–75 years	78 (38)	76 (36)
> 75 years	4 (2)	4 (2)
Sex [F/M], %	44/56	41/59
Family origin		
Native American or Alaska Native	1 (< 1)	1 (< 1)
Asian	16 (8)	20 (10)
Black or African American	6 (3)	7 (3)
White	157 (76)	157 (74)
Not reported	28 (14)	26 (12)
ECOG PS at baseline[a], n (%)		
0	114 (55)	121 (57)
1	93 (45)	89 (42)
2	1 (< 1)	1 (< 1)
Myeloma type (immunofixation), n (%)		
IgG	113 (54)	108 (51)
IgA	37 (18)	37 (18)
IgM	0	1 (< 1)
IgD	2 (1)	2 (< 1)
IgE	0	0
Light chain	47 (23)	56 (27)
Kappa	25 (12)	27 (13)
Lambda	22 (11)	29 (14)
Biclonal	1 (< 1)	2 (< 1)
Negative immune fixation	8 (4)	5 (2)
ISS stage at baseline[b], n (%)		
I	136 (65)	132 (63)
II	60 (29)	65 (31)
III	12 (6)	14 (7)

Table 10: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd (multipage table)

Study characteristic category	**Ciltacabtagene autoleucel N = 208**	**Individualized treatment choosing from DPd or PVd N = 211**
Disease duration: time between first diagnosis of multiple myeloma and randomization [years],		
Mean (SD)	3.9 (2.9)	4.3 (3.2)
Median [Q1; Q3]	3.0 [2.0; 5.0]	3.4 [2.1; 5.7]
Number of lytic bone lesions, n (%)		
0	41 (20)	64 (30)
1–10	79 (38)[c]	76 (36)[c]
> 10	88 (42)	71 (34)
Presence of soft tissue plasmacytomas, n (%)		
Yes	44 (21)	35 (17)
No	164 (79)	176 (83)
Cytogenetic risk, n (%)		
Standard risk	69 (33)	70 (33)
High risk	123 (59)	132 (63)
del(17p)	49 (24)	43 (21)
t(4;14)	30 (15)	30 (14)
t(14;16)	3 (1)	7 (3)
Gain/amp(1q)	89 (43)	107 (51)
Unknown	15 (7)	8 (4)
Number of prior therapies, n (%)		
1	68 (32.7)	68 (32.2)
2	83 (39.9)	87 (41.2)
3	57 (27.4)	56 (26.5)
Stem cell transplantation in prior therapy, n (%)		
Autologous	171 (82.2)	185 (87.7)
Once	157 (75.5)	173 (82.0)
Twice	14 (6.7)	12 (5.7)
Allogeneic	3 (1.4)	1 (0.5)
Treatment discontinuation, n (%)	0 (0)[d]	165 (78[c])[e]
Study discontinuation, n (%)[f]	51 (25)	87 (41)

Table 10: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd (multipage table)

Study characteristic category	Ciltacabtagene autoleucel N = 208	Individualized treatment choosing from DPd or PVd N = 211

a. The last non-missing ECOG PS on or before apheresis/Cycle 1 Day 1 is listed. All patients met the inclusion criterion of an ECOG PS of 0 or 1 prior to randomization.
b. The ISS stage is determined on the basis of serum ß2-microglobulin and albumin.
c. Institute's calculation.
d. As ciltacabtagene autoleucel is a single infusion, this therapy cannot be discontinued. However, 12 (6%) of the randomized patients in the intervention arm received leukapheresis but no ciltacabtagene autoleucel infusion. This was due to disease progression (10 [5%]) and death (2 [1%]).
e. The most common reason for treatment discontinuation in the control arm was disease progression (68%) (percentages based on randomized patients). The data also include patients who died during treatment with the study medication (3%). Moreover, 3 of the randomized patients never started treatment.
f. The data include patients who died during the treatment with the study medication (intervention arm: 50 [24%] vs. control arm: 82 [39]).

DPd: daratumumab in combination with dexamethasone; ECOG PS: Eastern Cooperative Oncology Group Performances Status; f: female; IgA: immunoglobulin A; IgD: immunoglobulin D; IgE: immunoglobulin E; IgG: immunoglobulin G; IgM: immunoglobulin M; ISS: International Staging System; m: male; n: number of patients in the category; N: number of randomized patients; PVd: pomalidomide in combination with bortezomib and dexamethasone; Q1: 1st quartile; Q3: 3rd quartile; RCT: randomized controlled trial; SD: standard deviation

The patient characteristics are largely comparable in the two treatment arms. Patients were 60 years of age on average and predominantly white (75%). Across both study arms, the proportion of men was around 58%. The majority (94%) of the patients included had a disease categorized as stage I or II according to the ISS. In the intervention arm, the proportion of patients with more than 10 lytic bone lesions was higher than in the control arm (42% vs. 34%), whereas the proportion of patients with a standard cytogenetic risk was the same in both arms and was 33% in each case.

In the CARTITUDE-4 study, around 33% of patients had received 1 prior therapy, around 41% had 2 prior therapies and around 27% had 3 prior therapies. Around 85% of the included patients had at least 1 autologous stem cell transplantation (of which approx. 6% had 2 transplantations) as prior therapy. Allogeneic stem cell transplantation was only used sporadically in the pretreatment.

In the intervention arm, 6% of patients did not receive ciltacabtagene autoleucel infusion despite leukapheresis. The reasons for this were disease progression (5%) or death (1%). In the control arm, around 78% of patients discontinued treatment. The most common reason for this was disease progression (68%). The proportion of patients with study discontinuation

was lower in the intervention arm than in the control arm (25% versus 41%). Thereby, the data on study discontinuation mainly include deaths (24% vs. 39%).

Information on the course of the study

Table 11 shows the mean/median treatment duration of the patients and the mean/median observation period for individual outcomes.

Table 11: Information on the course of the study – RCT, direct comparison: ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd (multipage table)

Study **duration of the study phase** **outcome category/outcome**	**Ciltacabtagene autoleucel** **N = 208**	**Individualized treatment choosing from DPd or PVd** **N = 211**
CARTITUDE-4		
Treatment duration [months]		
Median [min; max]	2.6 [1.5; 8.1][a, b]	11.5 [0.5; 44.0] DPd: 12.3 [0.5; 44.0] PVd: 4.8 [0.5; 29.6]
Mean (SD)	2.6 (0.7)[a, b]	overall: ND DPd: 16.2 (12.6) PVd: 8.9 [8.6]
Observation period [months]		
Overall survival[c]		
Median [Q1; Q3]	33.7 [29.0; 35.4]	33.5 [16.6; 34.6]
Mean (SD)	28.8 (11.3)	26.3 (11.4)
Morbidity		
EORTC QLQ-C30, PGIS		
Median [Q1; Q3]	23.5 [ND]	8.5 [ND]
Mean (SD)	ND	ND
EQ-5D VAS		
Median [Q1; Q3]	23.4 [ND]	8.6 [ND]
Mean (SD)	ND	ND
Health-related quality of life		
EORTC QLQ-C30		
Median [Q1; Q3]	23.5 [ND]	8.5 [ND]
Mean (SD)	ND	ND

Table 11: Information on the course of the study – RCT, direct comparison: ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd (multipage table)

Study duration of the study phase outcome category/outcome	**Ciltacabtagene autoleucel N = 208**	**Individualized treatment choosing from DPd or PVd N = 211**
Side effects		
AEs, SAEs, severe AEs[d] and other outcomes on AEs[e]		
Median [Q1; Q3]	32.2 [ND]	30.6 [ND]
Mean (SD)	ND	ND
PRO-CTCAE		
Median [Q1; Q3]	23.4 [ND]	8.6 [ND]
Mean (SD)	ND	ND

a. The time from leukapheresis to infusion of ciltacabtagene autoleucel is listed.
b. Institute's calculation.
c. Calculation of medians using the inverse Kaplan-Meier method.
d. Operationalized according to CTCAE grade ≥ 3.
e. The company's information also includes the period in which only events were recorded for which the investigator suspected a connection with the study medication and in which only certain events were recorded for the individual patients (i.e. only AEs of special interest).

CTCAE: Common Terminology Criteria for Adverse Events; DPd: daratumumab in combination with pomalidomide and dexamethasone; EORTC: European Organisation for Research and Treatment of Cancer; max: maximum; min: minimum; N: number of randomized patients; ND: not data; PGIS: Patient's Global Impression of Severity; PRO-CTCAE: Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; PVd: pomalidomide in combination with bortezomib and dexamethasone; Q1: 1st quartile; Q3: 3rd quartile; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

For the intervention arm, data are available on the time from leukapheresis to infusion of ciltacabtagene autoleucel as treatment duration. The median duration is 2.6 months. The median treatment duration in the control arm was 11.5 months, with this being longer for DPd (12.3 months) than for PVd (4.8 months).

The observation period for overall survival is comparable between the treatment arms and is around 33.5 months. For the outcomes in the morbidity and health-related quality of life categories, the observation periods in the CARITITUDE-4 study are both significantly shorter overall compared to the observation period of the outcome of overall survival and also differ greatly between the treatment arms, with shorter observation periods in the control arm (approx. 23.5 months in the intervention arm vs. approx. 8.5 months in the control arm). This also applies to the outcome of health status recorded using the EQ-5D VAS, which the study design had planned to be recorded until the end of the study (see Table 9), but whose median observation period does not differ significantly from that of the other patient-reported outcomes and which is significantly shorter, especially in the control arm (see Table 11). The

company does not justify this deviation between the planned and the actual observation period in the dossier. Since the results of the patient-reported outcomes are not suitable for the benefit assessment in the present data situation (see Section I 4.1 for explanation), this does not entail any consequence.

The company states in contrast to the patient-reported outcomes that observation durations for outcomes in the side effects category in the intervention arm (32.2 months) and in the control arm (30.6 months) are comparable both with the observation duration for overall survival and also between the treatment arms. However, the information provided by the company also includes the periods in which the AEs were no longer recorded completely, but only selectively (due to a suspected causal relationship or the longer recording of AEs of special interest; see also Table 9). Accordingly, the observation periods for the outcomes on side effects are overestimated (for the consequences for the benefit assessment, see comments on the analyses on AEs presented by the company in Section I 4.1)

Subsequent therapies

Table 12 shows the subsequent therapies patients received after discontinuing the study medication.

Table 12: Information on subsequent antineoplastic therapies (≥ 1% of the patients in ≥ 1 treatment arm) – RCT, direct comparison: ciltacabtagene autoleucel versus individualized treatment choosing from DPd or PVd (multipage table)

Study **drug class** **drug**	**Patients with subsequent therapy, n (%)**	
	ciltacabtagene autoleucel **N = 208**	**individualized treatment choosing from DPd or PVd** **N = 211**
CARTITUDE-4		
Total	65 (31.3)	146 (69.2)
Alkylating agents	36 (55.4[a])	75 (51.4[a])
Cyclophosphamide	33 (50.7[a])	70 (47.9[a])
Bendamustine	1 (1.5[a])	9 (6.2[a])
Melphalan	5 (7.7[a])	7 (4.8[a])
Carmustine	2 (3.1[a])	1 (0.7[a])
Antimetabolites	20 (30.8[a])	31 (21.2[a])
Fludarabine	20 (30.8[a])	27 (18.5[a])
Cytarabine	0 (0)	4 (2.7[a])
Methotrexate	0 (0)	4 (2.7[a])
Cytotoxic antibiotics and related substances	14 (21.5[a])	29 (19.9[a])
Doxorubicin	14 (21.5[a])	29 (19.9[a])
Monoclonal antibodies and antibody-drug conjugates	36 (55.4[a])	86 (58.9[a])
Teclistamab	5 (7.7[a])	32 (21.9[a])
Talquetamab	10 (15.4[a])	28 (19.2[a])
Belantamab mafodotin	5 (7.7[a])	19 (13.0[a])
Daratumumab	14 (21.5[a])	15 (10.3[a])
Elotuzumab	2 (3.1[a])	5 (3.4[a])
Antineoplastic monoclonal antibodies	1 (1.5[a])	4 (2.7[a])
Cevostamab	2 (3.1[a])	4 (2.7[a])
Elranatamab	1 (1.5[a])	4 (2.7[a])
Isatuximab	11 (16.9[a])	2 (1.4[a])

Table 12: Information on subsequent antineoplastic therapies (≥ 1% of the patients in ≥ 1 treatment arm) – RCT, direct comparison: ciltacabtagene autoleucel versus individualized treatment choosing from DPd or PVd (multipage table)

Study **drug class** **drug**	**Patients with subsequent therapy, n (%)**	
	ciltacabtagene autoleucel **N = 208**	**individualized treatment choosing from DPd or PVd** **N = 211**
Other antineoplastic agents	47 (72.3[a])	106 (72.6[a])
Carfilzomib	20 (30.8[a])	72 (49.3[a])
Bortezomib	11 (16.9[a])	32 (21.9[a])
Cisplatin	15 (23.1[a])	24 (16.4[a])
CAR T cells, NOS	1 (1.5[a])	18 (12.3[a])
Selinexor	2 (3.1[a])	15 (10.3[a])
Idecabtagene vicleucel	0 (0)	11 (7.5[a])
Ciltacabtagene autoleucel	20 (30.8[a])[b]	8 (5.5[a])
Mezigdomide	2 (3.1[a])	4 (2.7[a])
Ixazomib	1 (1.5[a])	3 (2.1[a])
Nirogacestat	0 (0)	3 (2.1[a])
Venetoclax	2 (3.1[a])	1 (0.7[a])
Vegetable alkaloids and other natural substances	17 (26.2[a])	29 (19.9[a])
Etoposide	14 (21.5[a])	25 (17.1[a])
Vincristine	3 (4.6[a])	4 (2.7[a])
Corticosteroids for systemic use	45 (69.2[a])	108 (74.0[a])
Dexamethasone	45 (69.2[a])	103 (70.5[a])
Prednisolone	0 (0)	4 (2.7[a])
Prednisone	0 (0)	2 (1.4[a])
Immunosuppressants	21 (32.3[a])	36 (24.7[a])
Pomalidomide	18 (27.7[a])	23 (15.8[a])
Thalidomide	2 (3.1[a])	6 (4.1[a])
Lenalidomide	2 (3.1[a])	5 (3.4[a])
Investigational preparation	5 (7.7[a])	23 (15.8[a])

a. Institute's calculation based on the proportion of patients with subsequent therapy.
b. Patients who received ciltacabtagene autoleucel following disease progression under the bridging therapy as part of the study were categorized as patients with subsequent therapy in accordance with the study design.

CAR: chimeric antigen receptor; DPd: daratumumab in combination with pomalidomide and dexamethasone; n: number of patients with subsequent therapy; N: number of randomized patients; NOS: not otherwise specified; PVd: pomalidomide in combination with bortezomib and dexamethasone; RTC: randomized controlled trial

The CARTITUDE-4 study involved no restrictions regarding subsequent antineoplastic therapies. The study protocol did not provide for any switching of patients from the control arm into the intervention arm due to disease progression. Patients in the intervention arm who experienced disease progression during the bridging therapy could continue to receive ciltacabtagene autoleucel within the framework of the study. According to the study design, this was categorized as subsequent therapy. For the present assessment, however, it is assumed that in the intervention arm, treatment with ciltacabtagene autoleucel is also carried out in the event of disease progression under the bridging therapy as part of the current line of treatment, and therefore does not represent a subsequent therapy.

In the dossier, information on subsequent antineoplastic therapies is only available at drug level and aggregated across all subsequent therapies. For a better assessment of guideline-compliant use, information on the treatment regimens used in the individual treatment lines would be preferable to information at drug level aggregated across all treatment lines in the present therapeutic indication.

At the data cut-off of 01 May 2024, 68 patients in the intervention arm and 147 patients in the control arm had disease progression. Of these, 65 patients in the intervention arm and 146 patients in the control arm received at least one subsequent therapy. Thereby, the data in the intervention arm include 20 (30.8%) patients who received ciltacabtagene autoleucel after disease progression during bridging therapy. However, contrary to the information in the study planning, it is assumed for the present assessment that treatment with ciltacabtagene autoleucel in these patients does not represent a subsequent therapy, but rather a continuation of the planned treatment concept. Since the observation for outcomes in the side effects category partly ended with the start of subsequent therapy (for details see Table 9 in Section I 3.2), the company's approach of categorizing treatment with ciltacabtagene autoleucel as subsequent therapy in this patient group makes it even more difficult to assess the suitability of the analyses available for outcomes in the side effects category (see comments on the analyses on AEs presented by the company).

Overall, the other therapies administered in the intervention and control arm reflect the diversity of treatment options in the therapeutic indication. In both treatment arms, established drugs such as carfilzomib as well as novel drugs such as monoclonal antibodies or CAR-T cells, which had not been exhausted as treatment options in the previous therapies, were preferentially used within the framework of the subsequent therapies.

Risk of bias across outcomes (study level)

Table 13 shows the risk of bias across outcomes (risk of bias at study level).

Table 13: Risk of bias across outcomes (study level) – RCT, direct comparison: ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
CARTITUDE-4	Yes	Yes	No	No	Yes	Yes	Low

DPd: Daratumumab in combination with pomalidomide and dexamethasone; PVd: pomalidomide in combination with bortezomib and dexamethasone; RCT: randomized controlled trial

The risk of bias across outcomes was rated as low for the CARTITUDE-4 study.

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

Transferability of the study results to the German health care context

The company described that the CARTITUDE-4 study was conducted in 88 study centres in 16 countries. It states that 61% and thus the majority of the included patients come from Europe and around 75% are of Caucasian origin. Moreover, from the company's point of view, there were no signs of biodynamic or kinetic differences between the individual population groups or countries involved and Germany to the extent that they would have a significant impact on the study results.

According to the company, the study population of the CARTITUDE-4 study basically comprises patients from the 2nd line of treatment onwards. In the company's view, the prior therapies of the included patients generally correspond to the treatment pathways observed in German health care reality when considering the entire study population. The company therefore assumes the results to be transferable to the German health care context.

The company did not provide any further information on the transferability of the study results to the German health care context. For the transferability of the study results, see also Section I 4.2.

I 4 Results on added benefit

I 4.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - symptoms, recorded using the EORTC QLQ-C30 and the PGIS.
  - health status, recorded using the EQ-5D VAS
- Health-related quality of life
  - recorded using the EORTC QLQ-C30
- Side effects
  - SAEs
  - severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to AEs
  - PRO-CTCAE
  - cytokine release syndrome
  - severe neurological toxicity
  - infusion related reactions
  - severe infections
  - secondary malignancies
  - other 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 14 shows the outcomes for which data are available in the included study.

Table 14: Matrix of the outcomes – RCT, direct comparison: ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd

Study	Outcomes													
	Overall survival	Symptoms	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	PRO-CTCAE	Cytokine release syndrome	Severe neurological toxicity	Infusion related reactions	Severe infections	Secondary malignancies	Other specific AEs
CARTITUDE-4	Yes	No[b]	No[b]	No[b]	No[b]	Yes	Yes	No[b]	No[b]	No[b]	No[b]	No[b]	No[b]	No[c]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. No suitable data available; see the following text section for reasons.
c. No suitable analyses on AEs available, a choice of specific AEs is therefore impossible; for reasons, see the following section.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; DPd: daratumumab in combination with pomalidomide and dexamethasone; EORTC: European Organisation for Research and Treatment of Cancer; PGIS: Patient Global Impression of Severity; PRO-CTCAE: Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; PVd: pomalidomide in combination with bortezomib and dexamethasone; QLQ-C30: Quality of Life Questionnaire - Core30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

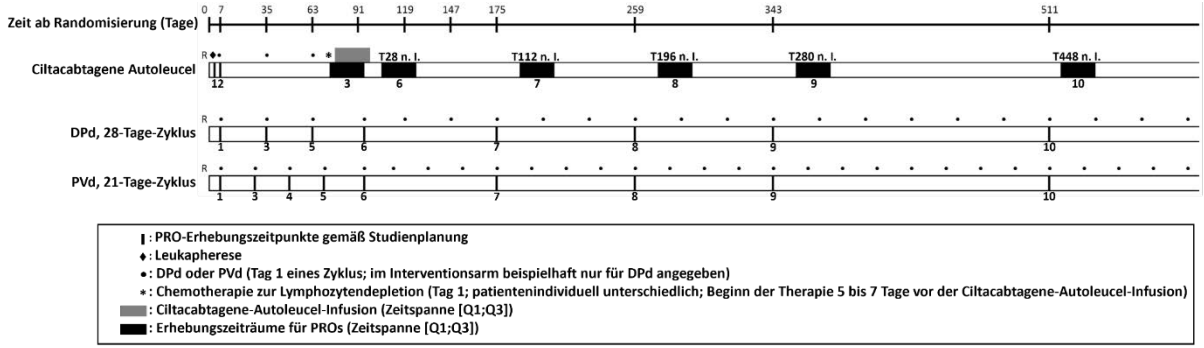
Notes on the outcomes

Notes on the recording of patient-reported outcomes

In Module 4 A of the dossier, the company presents responder analyses for all patient-reported outcomes for the time until the first or confirmed deterioration/improvement. Moreover, in the study documents, continuous analyses using a mixed-effects model repeated measures (MMRM) are available for selected patient-reported outcomes on morbidity and health-related quality of life for the change from baseline. However, both the responder analyses presented by the company in Module 4 A of the dossier and the continuous analyses available in the study documents are not suitable for the present benefit assessment, as the patient-relevant outcomes were not recorded in relevant sections of the CAR T-cell therapy in the intervention arm. This is explained below.

Lack of recording of patient-reported outcomes in relevant periods of CAR T cell therapy

Figure 1 shows a schematic overview of the time points of recording of patient-reported outcomes in the CARTITUDE-4 study.



Zeit ab Randomisierung (Tage)	Time from randomization (days)	PRO-Erhebungszeitpunkte gemäß Studienplanung	PRO recording time points according to study design
DPd, 28-Tage-Zyklus	DPd, 28-day cycle	Leukapherese	Leukapheresis
PVd, 21-Tage-Zyklus	PVD, 21-day cycle	DPd oder PVd (Tag 1 eines Zyklus: im Internventionsarm beispielhaft nur für DPd angegeben)	DPd or PVd (Day 1 of a cycle: in the intervention arm only provided for DPd as an example
		Chemotherapie zur Lymphozytendepletion (Tag 1; patientenindividuell unterschiedlich, Beginn der Therapie 5 bis 7 Tage vor der Ciltacabtagene-Autoleucel-Infusion	Lymphodepleting chemotherapy (Day 1; differing between individual patients, start of treatment 5 to 7 days prior to the ciltacabtagene autoleucel infusion)
		Ciltacabtagene-Autoleucel-Infusion (Zeitspanne [Q1; Q3])	Ciltacabtagene autoleucel infusion (time span [Q1; Q3])
		Erhebungszeiträume für PROs (Zeitspanne [Q1; Q3])	Recording time points for PROs (time span [Q1; Q3])

D: day; DPd: daratumumab in combination with pomalidomide and dexamethasone; fI: following infusion; PRO: patient-reported outcome; PVd: pomalidomide in combination with bortezomib and dexamethasone; Q1: 1st quantile; Q3: 3rd quantile; R: randomization

Figure 1: Schematic presentation of the planned and extrapolated recording time points for patient-reported outcomes in the CARTITUDE-4 study.

In the intervention arm, the recording of patient-reported outcomes began within 72 hours before leukapheresis, which was to take place 3 to 6 days after randomization, closely followed by a recording on Day 1 of the first cycle of bridging therapy (7 days after randomization at the latest). Thereafter, there will be only one recording on Day 1 of lymphodepleting chemotherapy in the intervention arm, and then again on Day 28 after the infusion of ciltacabtagene autoleucel. This means that neither the treatment period in which the bridging therapy is administered nor other phases such as the period between lymphodepleting chemotherapy and CAR T cell infusion or the period immediately after the infusion are taken into account in the intervention arm. However, these treatment phases are part of the treatment concept in the intervention arm, and the associated burden to the patients must therefore be taken into account in the recording of patient-reported outcomes. In the control arm, in contrast, patient-reported outcomes are recorded continuously and more frequently immediately from the start of treatment after randomization, which means that the burden of the therapy is continuously recorded. A fair comparison of the two therapy concepts is therefore not possible.

MMRM analyses not suitable

In the study documents, analyses using MMRM are available for selected patient-reported outcomes on morbidity and health-related quality of life for the change from baseline. However, these analyses only take into account recording time points in the two study arms that can be assigned to each other in terms of time (recording time points 1, 2 and 6 for the intervention arm, recording time points 1 and 6 for the control arm; see Figure 1). The proportion of patients included in these analyses differs significantly between the study arms. At the 1st subsequent recording in the intervention arm (i.e. recording time point 2 in Figure 1), for example, the response rate for the EORTC QLQ-C30 is around 85% related to the patients who have not died at this time, while in the control arm only around 67% have a 1st subsequent recording (corresponds to recording time point 6 in Figure 1). In addition to the deficiencies already described above, the continuous analyses are therefore not suitable for the benefit assessment due to highly differentiated responses.

Conclusion on analyses of patient-reported outcomes

The differences in the time points of recording caused by the study design therefore do not allow a fair comparison of the treatment concepts in the treatment arms. Overall, the results for the patient-reported outcomes of the CARTITUDE-4 study are therefore not meaningfully interpretable due to the recording scheme. This concerns both the responder analyses on the time to first or confirmed deterioration/improvement presented by the company in Module 4 A of the dossier and the continuous analyses available in the study documents. There are also highly differentiated responses for the continuous analyses.

Further comments on patient-reported outcomes

In addition to the previously described points of criticism regarding the recording of patient-reported outcomes, there are the following further points of criticism for individual outcomes:

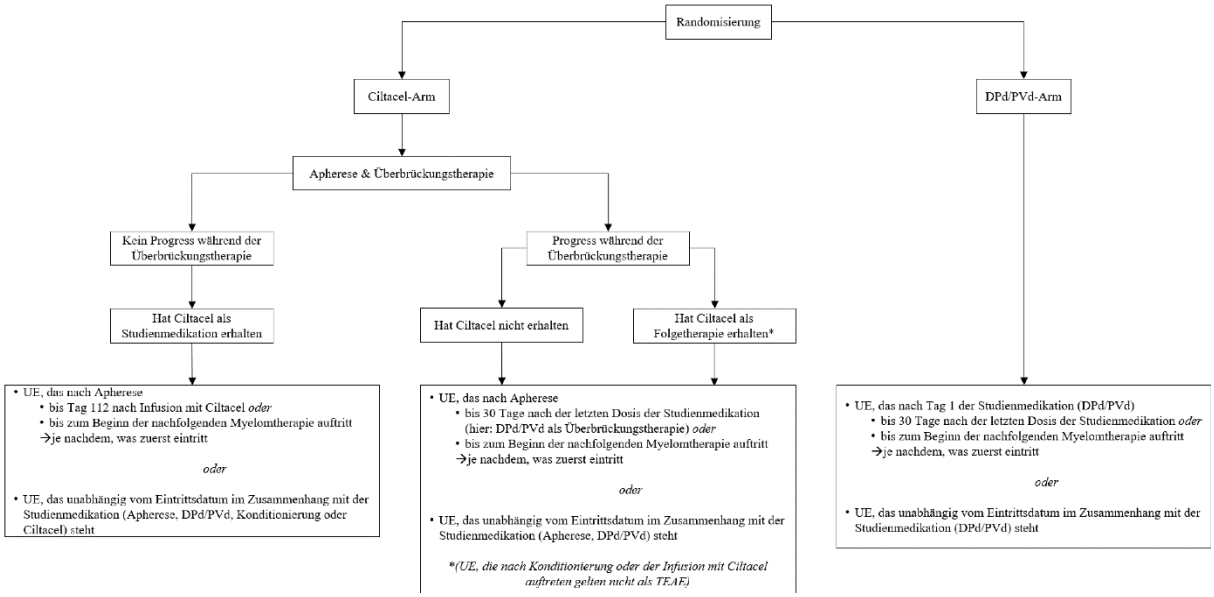
- Although, according to the study design, the outcome of health status (recorded using the EQ-5D VAS) was planned to be recorded until the end of the study, the data on the course of the study show that the median observation period of this outcome does not differ significantly from that of the other patient-reported outcomes and which is significantly shortened, especially in the control arm (see Table 11 in Section I 3.2). Although it is positive to note that, in contrast to the other patient-reported outcomes, the outcome should categorically be observed until the end of the study, it remains unclear why the median observation period was shortened, particularly in the control arm. The company does not provide any corresponding justification in its dossier.
- In the CARTITUDE-4 study, the patient-reported Multiple Myeloma Symptom and Impact Questionnaire (MySIm-Q) developed by the company is used to record symptoms of multiple myeloma and impairments caused by the symptoms. The MySIm-Q comprises a total of 17 items, each of which is rated on a 5-point Likert scale (0 = best possible condition to 4 = worst possible condition). According to the company, 11 of these items address the symptoms and 6 items address the impairment of activity, social life and emotional aspects. In Module 4 A of the dossier, the company presents analyses on the total symptom score, which summarizes the results of the symptoms items, as well as analyses of the total impact score, which summarizes the results of the impairment items. However, from the sources on the development of the MySIm-Q presented by the company in the dossier, it cannot be deduced that it can be used as a valid instrument for the recording of symptoms and impairments in patients with multiple myeloma. This is due to the fact that the MySIm-Q has not yet been fully validated; in particular, the dossier lacks information on investigations of the psychometric properties of the total impact score.
- In Module 4 A of the dossier, the company presents additional analyses based on a selection of the PRO-CTCAE item library. It states that, according to the study design, pre-specified items that are common AEs in patients with multiple myeloma were recorded and names nausea, vomiting, diarrhoea, shortness of breath, rash, dizziness, headache and fatigue/tiredness/lack of energy. It remains unclear whether this selection ensures the recording of all important potential AEs of the drugs used in the intervention and control arm. In Module 4 A of the dossier, the company itself also describes that the selection of the prespecified items was not systematic, and for this reason it only presents the analyses as supplementary information and does not include them in its assessment.

Side effects

Comments on the analyses of AEs presented by the company

In the CARTITUDE-4 study, AEs, the severe AEs based on them (CTCAE grade ≥ 3) and SAEs are recorded in full for different lengths of time for the patients between the two treatment arms (i.e. without selective observation of AEs due to suspected causal relationships or AEs of special interest). The study documents contain discrepant data on the period over which all events were recorded in full (for a detailed explanation, see Section I 3.2).

The analyses presented by the company in the dossier on the outcomes in the side effects category again include follow-up durations that deviate from the planned observation periods (see Figure 2). Particularly in the intervention arm, not all observation periods are included in which, according to the study design, a complete recording of all events was planned for the individual patients.



AE: adverse event; Ciltacel: ciltacabtagene autoleucel; DPd: daratumumab in combination with pomalidomide and dexamethasone; PVd: pomalidomide in combination with bortezomib and dexamethasone; TEAE: treatment emergent adverse event

Randomisierung:	Randomization
Ciltacel-Arm	Ciltacel arm
DPd/PVd-Arm	DPd/PVd arm
Apherese und Überbrückungstherapie:	Apheresis and bridging therapy
Kein Progress während der Überbrückungstherapie:	No progress during bridging therapy
Progress während der Überbrückungstherapie:	Progress during bridging therapy
Hat Ciltacel als Studienmedikation erhalten:	Received ciltacel as study medication
Hat Ciltacel nicht erhalten:	Did not receive ciltacel
Hat Ciltacel als Folgetherapie erhalten:	Received ciltacel as subsequent therapy
UE, das nach Apherese • bis Tag 112 nach Infusion mit Ciltacel oder: • bis zum Beginn der nachfolgenden Myelomtherapie auftritt: • je nachdem, was zuerst eintritt:	AE occurring following apheresis until Day 112 after ciltacel infusion or until the start of subsequent myeloma therapy whichever occurs first
oder	or
UE, das unabhängig vom Eintrittsdatum im Zusammenhang mit der Studienmedikation (Apherese, DPd/PVd, Konditionierung oder Ciltacel) steht:	AE which is associated with the study medication (apheresis, DPd/PVd, conditioning or ciltacel) irrespective of the time of occurrence
UE, das nach Apherese bis 30 Tage nach der letzten Dosis der Studienmedikation (hier: DPd/PVd als Überbrückungstherapie) oder • bis zum Beginn der nachfolgenden Myelomtherapie auftritt: • je nachdem, was zuerst eintritt:	AE occurring following apheresis until 30 days following the last study medication (here: DPd/PVd as bridging therapy, or until the start of subsequent myeloma therapy whichever occurs first
oder	or
UE, das unabhängig vom Eintrittsdatum im Zusammenhang mit der Studienmedikation (Apherese, DPd/PVd) steht:	AE which is associated with the study medication (apheresis, DPd/PVd) irrespective of the time of occurrence
(UE, die nach Konditionierung oder der Infusion mit Ciltacel auftreten, gelten nicht als TEAE)	(AEs occurring after conditioning or ciltacel infusion are not considered a TEAE)
UE, das nach Tag 1der Studienmedikation (DPd/PVd) • bis bis 30 Tage nach der letzten Dosis der Studienmedikation oder: • bis zum Beginn der nachfolgenden Myelomtherapie auftritt: • je nachdem, was zuerst eintritt:	AE occurring after Day 1 of the study medication (DPd/PVd) until 30 days following the last dose of the study medication,or until the start of subsequent myeloma therapy whichever occurs first
oder	or
UE, das unabhängig vom Eintrittsdatum im Zusammenhang mit der Studienmedikation (DPd/PVd) steht:	AE which is associated with the study medication (DPd/PVd) irrespective of the time of occurrence

Figure 2: Illustration of the observation periods or events in the outcomes of the side effects category from the CARTITUDE-4 study considered for the analyses of the company (taken from Module 4 A of the company)

The company's information shows that AEs, SAEs or severe AEs from different observation periods are considered in the intervention arm, depending on whether a patient received or did not receive ciltacabtagene autoleucel or only received it after disease progression during bridging therapy. In the control arm, however, events are considered up to 30 days after the last dose of the comparator therapy or the start of a subsequent therapy, whichever comes first. In addition, events up to the end of the study for which the investigators suspected a causal relationship with the study medication were taken into account in both treatment arms.

The company's approach was inadequate for several reasons. In both treatment arms, AEs, SAEs and serious AEs recorded after the end of the complete survey were also taken into account if the investigator suspected a causal relationship with the study medication. In addition, selective recording of certain events for AEs of special interest was planned according to the study design after the complete recording of all AEs, although it remains unclear whether or not these recordings are included in the analyses presented by the company. The assessment of the causal relationship and possibly the selective recording of AEs of special interest results in incomplete and selective consideration of AEs in the analyses. This does not provide a complete picture of all events that have occurred. It cannot be assessed to what extent the two aspects described affect the results of the outcomes on the overall rate of SAEs and on common AEs, SAEs and severe AEs at the level of the System Organ Classes (SOCs) and the Preferred Terms (PTs).

Overall, the analyses presented for the superordinate outcome of SAEs and all analyses at SOC and PT level are not suitable for the benefit assessment due to the consideration of time periods in which only a selective survey of certain events per patient was conducted. The analyses for the superordinate outcome “severe AEs” are an exception. Although it is also assumed for this outcome that events were selectively recorded after the end of the complete survey, it is not assumed on the basis of the Kaplan-Meier curves with a high proportion of early events (see I Appendix B.2) that the described deficiencies call the observed result into question.

The present benefit assessment would require analyses of AEs, SAEs and serious AEs, which include all events in both treatment arms up to the end of the maximum observation period, in which a complete survey of all events for the individual patients was conducted. In addition, analyses with censoring from the administration of subsequent therapies should be presented. It should be noted that for patients in the intervention arm, treatment with ciltacabtagene autoleucel after disease progression under bridging therapy is not to be considered as subsequent therapy (for an explanation, see the use of bridging therapies in the CARTITUDE-4 study in Section I 3.2).

Overall, due to the existing uncertainties, it is not possible to assess whether the analyses described above are appropriate in the present, unclear data situation.

Discontinuation due to AEs

In the dossier, the company presents time-to-event analyses for the outcome of discontinuation due to AEs (discontinuation of at least 1 treatment component). In these analyses, events in the intervention arm are only taken into account up to the infusion of ciltacabtagene autoleucel. In contrast, discontinuation of treatment due to AEs caused by long-term therapy with DPd or PVd over a longer period of time was possible in the control arm. The analyses presented by the company are used for the benefit assessment, but the effect estimate only allows a conclusion to be drawn about a very shortened observation period for which data are available for both treatment arms (see Kaplan-Meier curves in I Appendix B.2).

Specific AEs

No suitable data are available in the company's dossier for the specific AEs of cytokine release syndrome, severe neurological toxicity, severe infections, secondary malignancies and infusion related reactions. There are both outcome-specific reasons and reasons across outcomes for this, which are listed below:

- It is unclear whether the analyses on specific AEs after a certain point in time also only selectively include events for which a suspected causal relationship exists. The only exceptions to this are secondary malignancies, which are planned to be completely recorded in both treatment arms until the end of the study according to the study design.
- For none of the specific AEs do the study documents show the operationalization, i.e. the SOCs or PTs or Standardized MedDRA Queries (SMQs) on the basis of which these outcomes should be recorded according to the study design. Due to the lack of specifications for the recording, it cannot be assumed that these outcomes were recorded uniformly within the framework of the study. Furthermore, it remains unclear whether these outcomes were recorded in the control arm in a comparable way to the intervention arm at all.
- In the intervention arm, the specific AEs cytokine release syndrome, severe neurological toxicity and severe infections were only recorded as of the infusion of ciltacabtagene autoleucel and do therefore not represent relevant treatment phases.
- According to the study design, infusion related reactions were not recorded separately in the CARTITUDE-4 study. The events underlying the outcome of infusion related reactions in the CARTITUDE-4 study were to be included in the analyses of AEs (overall rates and specific AEs). The assumption that individual specific AEs are symptoms of an

infusion related reaction is based on the plausibility of the symptoms and the typically early onset at the time of the first infusion with ciltacabtagene autoleucel or daratumumab. However, due to the unsuitability of the analyses on frequent AEs, SAEs and severe AEs presented by the company, it is not possible to map the events underlying the outcome of infusion related reactions via the specific AEs.

I 4.2 Risk of bias

Table 15 describes the risk of bias for the results of the relevant outcomes.

Table 15: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd

Study		Outcomes													
	Study level	Overall survival	Symptoms (EORTC QLQ-C30, PGIS)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	PRO-CTCAE	Cytokine release syndrome	Severe neurological toxicity	Infusion related reactions	Severe infections	Secondary malignancies	Other specific AEs
CARTITUDE-4	L	L	–[b]	–[b]	–[b]	–[b]	H[c]	H[d]	–[b]	–[b]	–[b]	–[b]	–[b]	–[b]	–[b]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. No suitable data available; for justification see Section I 4.1 of this dossier assessment.
c. Shortened observation periods due to potentially informative censoring.
d. Lack of blinding in subjective decision to discontinue.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; DPd: daratumumab in combination with pomalidomide and dexamethasone; EORTC: European Organisation for Research and Treatment of Cancer; H: high; L. low; PGIS: Patient Global Impression of Severity; PRO-CTCAE: Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; PVd: pomalidomide in combination with bortezomib and dexamethasone; QLQ-C30: Quality of Life Questionnaire - Core30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

The risk of bias for the result on overall survival was rated as low.

The risk of bias for the results on severe AEs was considered to be high. This is because the reasons that lead to a discontinuation of observation are potentially informative for the occurrence or observation of severe AEs.

The risk of bias for the results on discontinuation due to AEs is rated as high due to the subjective decision to discontinue in an unblinded study design.

Summary assessment of the certainty of conclusions

Taking into account the information provided by the company in Module 4 A of the dossier on the pretreatment and response of patients included in the CARTITUDE-4 study, it is assumed that the majority of patients included in the CARTITUDE-4 study received sufficient individualized treatment in the sense of the ACT. However, there are uncertainties, so it cannot be assumed that the comparator therapies used in the CARTITUDE-4 study represent a complete implementation of the ACT (for a detailed explanation, see the text section on the implementation of the ACT in the CARTITUDE-4 study in Section I 3.2). Moreover, it is unclear whether bridging therapy was indicated for all patients in the CARTITUDE-4 study. It therefore remains unclear whether the results of the study can be transferred without restriction to the German health care context, especially as there are clearly more treatment options available in health care and other patient-specific factors are taken into account in the treatment decision. Thus, at most hints, e.g. of an added benefit, can be derived for all outcomes irrespective of the outcome-specific risk of bias.

I 4.3 Results

Table 16 summarizes the results for the comparison of ciltacabtagene autoleucel with DPd or PVd in patients with relapsed and refractory multiple myeloma who had previously received at least 1 therapy, including 1 immunomodulator and 1 proteasome inhibitor, and who have experienced disease progression during the last therapy and are refractory to lenalidomide. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

The Kaplan-Meier curves on the time-to-event analyses are presented in I Appendix B of the full dossier assessment, and the results on common AEs, SAEs, severe AEs, and discontinuations due to AEs can be found in I Appendix C of the full dossier assessment.

Table 16: Results (mortality, morbidity, health-related quality of life and side effects) – RCT, direct comparison: ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd (multipage table)

Study outcome category outcome	Ciltacabtagene autoleucel		Individualized treatment choosing from DPd or PVd		Ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd
	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]
CARTITUDE-4					
Mortality					
Overall survival	208	NA 50 (24.0)	211	NA [37.75; NC] 83 (39.3)	0.55 [0.39; 0.79]; < 0.001[b]
Morbidity					
Symptoms (EORTC QLQ-C30, PGIS)	No suitable data[c]				
Health status (EQ-5D VAS)	No suitable data[c]				
Health-related quality of life					
EORTC QLQ-C30	No suitable data[c]				
Side effects					
AEs (supplementary information)	208	0.36 [0.26; 0.39] 208 (100)	208	0.30 [0.26; 0.36] 208 (100)	–
SAEs	No suitable data[c]				
Severe AEs[d]	208	0.85 [0.72; 0.89] 201 (96.6)	208	0.82 [0.69; 0.85] 202 (97.1)	0.94 [0.77; 1.16]; 0.580
Discontinuation due to AEs[e]	208	NA 6 (2.9)	208	NA [37.19; NC] 44 (21.2)	0.47 [0.18; 1.21]; 0.116
PRO-CTCAE	No suitable data[c]				
Cytokine release syndrome	No suitable data[c]				
Severe neurological toxicity	No suitable data[c]				
Infusion related reactions	No suitable data[c]				
Severe infections	No suitable data[c]				
Secondary malignancies	No suitable data[c]				

Table 16: Results (mortality, morbidity, health-related quality of life and side effects) – RCT, direct comparison: ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd (multipage table)

Study outcome category outcome	Ciltacabtagene autoleucel		Individualized treatment choosing from DPd or PVd		Ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd
	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]

a. HR, CI and p-value: Cox-PH model, stratified by comparator therapy of investigator's choice (DPd vs. PVd), ISS stage (I vs. II vs. III) and number of previous lines of treatment (1 vs. 2 or 3).
b. p-value: log-rank test, stratified by comparator therapy of investigator's choice (DPd vs. PVd), ISS stage (I vs. II vs. III) and number of prior lines of treatment (1 vs. 2 or 3).
c. See Section I 4.1 for reasons.
d. Operationalized as CTCAE grade ≥ 3.
e. Discontinuation of at least 1 treatment component; in the intervention arm, only events up to the infusion of ciltacabtagene autoleucel that led to the discontinuation of at least 1 treatment component of the bridging therapy are recorded.

AE: adverse event; CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Events; DPd: Daratumumab in combination with pomalidomide and dexamethasone; EORTC: European Organisation for Research and Treatment; HR: Hazard Ratio; ISS: International Staging System; n: number of patients with (at least 1) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PGIS: Patient Global Impression of Severity; PRO-CTCAE: Patient-Reported Outcomes version of the CTCAE; PVd: pomalidomide in combination with bortezomib and dexamethasone; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes (see also Section I 4.2).

Mortality

overall survival

A statistically significant difference between the treatment arms was shown for the outcome of overall survival.

When looking at the Kaplan-Meier curves for this outcome, it is noticeable that a clear separation in favour of the intervention arm only emerges in the later course from around Month 14 (see Figure 3). Up to about month 5, in contrast, the Kaplan-Meier curve tends to fall more sharply in the intervention arm than in the control arm. This suggests that some patients reap less benefit or no benefit at all from the intervention. The European regulatory authority has included a corresponding warning in the SPC. According to this warning, physicians considering treatment with ciltacabtagene autoleucel should assess the impact of

rapidly progressive disease on patients' suitability to receive CAR-T infusion. Some patients may not benefit from treatment with ciltacabtagene autoleucel as they are at increased risk of early death if the disease progresses rapidly during bridging therapy [14,15].

Overall, there is a hint of added benefit of ciltacabtagene autoleucel in comparison with individualized treatment selecting from DPd or PVd.

Morbidity

Symptoms (recorded using the EORTC QLQ-C30 and PGIS), health status (recorded using the EQ-5D VAS)

No suitable data are available for symptoms (recorded using the EORTC QLQ-C30 and the PGIS) and health status (recorded using the EQ-5D VAS), (for reasons, see Section I 4.1). In each case, there is no hint of added benefit of ciltacabtagene autoleucel in comparison with individualized treatment selecting from DPd or PVd; an added benefit is therefore not proven.

Health-related quality of life (recorded using EORTC QLQ-C30)

No suitable data are available for health-related quality of life (recorded using the EORTC QLQ-C30) (for justification, see Section I 4.1). There is no hint of added benefit of ciltacabtagene autoleucel in comparison with individualized treatment selecting from DPd or PVd; an added benefit is therefore not proven.

Side effects

SAEs

No suitable data are available for the outcome of SAEs (see Section I 4.1 for reasoning). There is no hint of greater or lesser harm from ciltacabtagene autoleucel in comparison with individualized treatment selecting from DPd or PVd; greater or lesser harm is therefore not proven for this outcome.

Severe AEs and discontinuation due to AEs

There was no statistically significant difference between treatment groups for either of the outcomes of severe AEs or discontinuation due to AEs. In each case, there is no hint of greater or lesser harm from ciltacabtagene autoleucel in comparison with individualized treatment selecting from DPd or PVd; greater or lesser harm is therefore not proven for these outcomes.

PRO-CTCAE

There are no suitable data for the outcome of PRO-CTCAE (for reasoning, see Section I 4.1). There is no hint of greater or lesser harm from ciltacabtagene autoleucel in comparison with individualized treatment selecting from DPd or PVd; greater or lesser harm is therefore not proven for this outcome.

Cytokine release syndrome, severe neurological toxicity, infusion related reactions, severe infections and secondary malignancies

No suitable data are available for each of the outcomes of cytokine release syndrome, severe neurological toxicity, infusion related reactions, severe infections and secondary malignancies (for reasoning, see Section I 4.1). In each case, there is no hint of greater or lesser harm from ciltacabtagene autoleucel in comparison with individualized treatment selecting from DPd or PVd; greater or lesser harm is therefore not proven for these outcomes.

I 4.4 Subgroups and other effect modifiers

The following characteristics were considered to be relevant in the present benefit assessment:

- age (< 65 years versus ≥ 65 years)
- sex (female versus male)
- ISS stage (I versus II versus III)

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

In the dossier, the company presents analyses on the prespecified subgroups < 65 years, 65 to 75 years and > 75 years for the characteristic of age. For the subgroup > 75 years, only 8 patients were included in these analyses. If possible, the subgroups 65 to 75 years and > 75 years were therefore summarized to the subgroup ≥ 65 years for the present benefit assessment, and the Institute conducts calculations for the interaction tests.

Using the methods described above, the available subgroup results did not reveal any effect modifications.

I 5 Probability and extent of added benefit

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

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

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Chapter I 4 (see Table 17).

Table 17: Extent of added benefit at outcome level: ciltacabtagene autoleucel vs. individualized treatment[a] (multipage table)

Outcome category **outcome**	**Ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd** **median time to event (months)** **HR [95% CI];** **p-value** **probability[b]**	**Derivation of extent[c]**
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	NA vs. NA 0.55 [0.39; 0.79]; p < 0.001 probability: “hint”	Outcome category: mortality CI_u < 0.85 added benefit, extent: “major”
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30, PGIS)	No suitable data	Lesser/added benefit not proven
Health status (EQ-5D VAS)	No suitable data	Lesser/added benefit not proven
Health-related quality of life		
Symptoms (EORTC QLQ-C30)	No suitable data	Lesser/added benefit not proven
Side effects		
SAEs	No suitable data	Greater/lesser harm not proven
Severe AEs	0.85 vs. 0.82 0.94 [0.77; 1.16]; p = 0.580	Greater/lesser harm not proven
Discontinuation due to AEs	NA vs. NA 0.47 [0.18; 1.21]; p = 0.116	Greater/lesser harm not proven
PRO-CTCAE	No suitable data	Greater/lesser harm not proven
Cytokine release syndrome	No suitable data	Greater/lesser harm not proven
Severe neurological toxicity	No suitable data	Greater/lesser harm not proven
Infusion related reactions	No suitable data	Greater/lesser harm not proven
Severe infections	No suitable data	Greater/lesser harm not proven
Secondary malignancies	No suitable data	Greater/lesser harm not proven

a. In the CARTITUDE-4 study, the investigators could choose from the drug combinations DPd and PVd.
b. Probability provided if a statistically significant and relevant effect is present.
c. Depending on the outcome category, estimations of effect size use different limits based on the upper limit of the confidence interval (CI_u).

Table 17: Extent of added benefit at outcome level: ciltacabtagene autoleucel vs. individualized treatment[a] (multipage table)

Outcome category **outcome**	**Ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd** **median time to event (months)** **HR [95% CI];** **p-value** **probability[b]**	**Derivation of extent[c]**
AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; DPd: daratumumab in combination with pomalidomide and dexamethasone; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; NA: not achieved; PGIS: Patient Global Impression of Severity; PRO-CTCAE: Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; PVd: pomalidomide in combination with bortezomib and dexamethasone; QLQ-C30: Quality of Life Questionnaire - Core 30; SAE: serious adverse event; VAS: visual analogue scale		

I 5.2 Overall conclusion on added benefit

Table 18 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 18: Positive and negative effects from the assessment of ciltacabtagene autoleucel compared with individualized treatment[a]

Positive effects	**Negative effects**
Outcomes with observation over the entire study duration	
Mortality ▪ overall survival: hint of an added benefit – extent: "major"	–
Outcomes with shortened observation period	
–	–
No suitable data are available for outcomes in the following categories: ▪ morbidity (EORTC QLQ-C30, PGIS, EQ 5D VAS) ▪ health-related quality of life (EORTC QLQ-C30) ▪ side effects ▫ SAE ▫ PRO-CTCAE ▫ cytokine release syndrome ▫ severe neurological toxicity ▫ infusion related reactions ▫ severe infections ▫ secondary malignancies	
a. In the CARTITUDE-4 study, the investigators could choose from the drug combinations DPd and PVd. DPd: daratumumab in combination with pomalidomide and dexamethasone; EORTC: European Organisation for Research and Treatment of Cancer; PGIS: Patient Global Impression of Severity; PRO-CTCAE: Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; PVd: pomalidomide in combination with bortezomib and dexamethasone; QLQ-C30: Quality of Life Questionnaire - Core 30; SAE: serious adverse event; VAS: visual analogue scale	

The overall picture shows a hint of an added benefit with the extent "considerable" for overall survival. The analyses available on the outcomes of the categories of morbidity, health-related quality of life and side effects are largely unsuitable for the present benefit assessment. The only exceptions to this are the analyses on the outcomes of severe AEs and discontinuation due to AEs. However, no disadvantages are expected to an extent that would completely challenge the positive effect in overall survival. However, the extent of the added benefit cannot be quantified due to the lack of data on other outcomes.

In summary, there is a hint of a non-quantifiable added benefit of ciltacabtagene autoleucel over the ACT for adult patients with relapsed and refractory multiple myeloma who have previously received 1 to 3 prior therapies, including 1 immunomodulator and 1 proteasome inhibitor, and who showed disease progression during the last therapy and are refractory to lenalidomide, and for whom DPd or PVd is an appropriate individualized treatment.

For adult patients with relapsed and refractory multiple myeloma who have previously received 1 to 3 prior therapies, including 1 immunomodulator and 1 proteasome inhibitor,

and who showed disease progression during the last therapy and are refractory to lenalidomide, and for whom DPd or PVd is not a suitable individualized treatment and for patients who have already received at least 4 prior therapies, no data are available from the CARTITUDE-4 study for the assessment of the added benefit of ciltacabtagene autoleucel compared with the ACT. An added benefit of ciltacabtagene autoleucel over the ACT is therefore not proven for patients with 1 to 3 prior therapies for whom DPd or PVd is not a suitable individualized treatment, and for patients with at least 4 prior therapies.

Table 19 summarizes the result of the assessment of added benefit of ciltacabtagene autoleucel in comparison with the ACT.

Table 19: Ciltacabtagene autoleucel – probability and extent of added benefit (multipage table)

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with relapsed and refractory multiple myeloma, who have received at least one prior therapy, including 1 immunomodulator and 1 proteasome inhibitor, who have demonstrated disease progression on the last therapy, and who are refractory to lenalidomide	Individualized treatment[b, c] choosing from ▪ daratumumab in combination with bortezomib and dexamethasone ▪ daratumumab in combination with carfilzomib and dexamethasone ▪ daratumumab in combination with pomalidomide and dexamethasone ▪ isatuximab in combination with carfilzomib and dexamethasone ▪ isatuximab in combination with pomalidomide and dexamethasoned ▪ elotuzumab in combination with pomalidomide and dexamethasoned ▪ pomalidomide in combination with bortezomib and dexamethasonee ▪ pomalidomide in combination with dexamethasonef, g ▪ carfilzomib in combination with dexamethasone ▪ panobinostat in combination with bortezomib and dexamethasonef ▪ bortezomib in combination with pegylated liposomal doxorubicinf, g ▪ bortezomib in combination with dexamethasonef, g ▪ daratumumab monotherapyf, h ▪ cyclophosphamide as monotherapy or in combination with dexamethasonef, h ▪ melphalan as monotherapy or in combination with prednisolone or prednisone[f, h] ▪ high-dose therapy with autologous stem cell transplantationi ▪ high-dose therapy with allogeneic stem cell transplantation[j, k] taking into account the general condition, the drugs and drug combinations used in the prior therapies as well as the type and duration of response to the respective prior therapies and the eligibility for stem cell transplantation[l, m]	▪ Patients with 1 to 3 prior therapies for whom DPd or PVd is a suitable individualized treatment: hint of a non-quantifiable added benefito ▪ patients with 1 to 3 prior therapies for whom DPd or PVd is not a suitable individualized treatment, and patients with ≥ 4 prior therapies: added benefit not proven

Table 19: Ciltacabtagene autoleucel – probability and extent of added benefit (multipage table)

Therapeutic indication	ACT[a]	Probability and extent of added benefit
a. Presented is the ACT specified by the G-BA. b. For the implementation of individualized treatment in a study of direct comparison, the investigators are expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons). c. According to the G-BA, the duration of response to the prior therapy is a criterion for the individualized treatment. In this respect, according to the generally recognized state of medical knowledge, unsuitability of retreatment with the drugs or drug combinations of the prior therapy is defined as disease progression under the respective prior therapy or a duration of response of less than 12 months after completion of the respective prior therapy. Accordingly, for patients with relapsed disease who show a response in the form of CR, VGPR and PR of more than 12 months after completion of the prior therapy, treatment using the drugs or drug combinations used in the prior therapy may also be a suitable treatment option. d. Only for patients with at least 2 prior therapies. e. Only for patients who are refractory to a CD38 antibody. f. Only for patients who have received at least 4 prior therapies. g. Only for at least double-refractory patients for whom triplet therapy is not suitable. h. Only for at least triple-refractory patients for whom triplet or doublet therapy is not suitable. i. Only for patients after 1 prior therapy for whom autologous stem cell transplantation is an option; after achieving remission. Autologous stem cell transplantation should be offered to all patients eligible for transplantation who have not undergone transplantation as part of first-line therapy. In addition, an autologous re-transplantation can be performed if the progression-free survival after the first transplantation generally lasted at least 18 months. j. Only for patients after 1 prior therapy for whom allogeneic stem cell transplantation is an option; after achieving remission. Allogeneic stem cell transplantation is a treatment option for patients with primary refractoriness and an early relapse after autologous stem cell transplantation. k. The requirements of the "G-BA guideline on the testing of allogeneic stem cell transplantation in multiple myeloma beyond first-line therapy" Gemeinsamer Bundesausschuss, 2017 #26}, the "G-BA's decision on measures of quality assurance for allogeneic stem cell transplantation in multiple myeloma (QS-B SZT MM)" [3] and §137c of the German Social Code Book V shall apply with regard to the use of allogeneic stem cell transplantation. l. According to the G-BA, unsuitability of triplet or doublet therapy should be justified based on refractoriness and comorbidity of the patients and taking into account the toxicity of the respective therapy. m. According to the G-BA, patients in the present therapeutic indication are assumed to generally continue antineoplastic treatment. Best supportive care is therefore not considered an ACT. o. The CARTITUDE-4 study included only patients with an ECOG PS of 0 or 1. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2. DPd: daratumumab in combination with pomalidomide and dexamethasone; ECOG-PS: Eastern Cooperative Oncology Group – Performance Status; G-BA: Federal Joint Committee; CD: cluster of differentiation; CR: complete response; PR: partial response; PVd: pomalidomide in combination with bortezomib and dexamethasone; SGB: Social Code Book; VGPR: very good partial response		

The assessment described above deviates from that of the company, which derives an indication of a considerable added benefit for all patients in this therapeutic indication,

irrespective of the line of treatment and the suitability of DPd or PVd as an individualized treatment.

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

Supplementary note

The result of the assessment deviates from the result of the G-BA's assessment conducted in the context of the market launch in 2023. There, the G-BA had determined a non-quantifiable added benefit of ciltacabtagene autoleucel for patients with at least 3 prior therapies according to the first approval (see Chapter 1). However, in said assessment, the added benefit had been regarded as proven by the approval irrespective of the underlying data because of the special situation for orphan drugs.

I 6 References for English extract

Please see full dossier assessment for full reference list.

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

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