Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Idecabtagen vicleucel (multiple myeloma, at least 3 prior therapies)

of 16 June 2022

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. For medicinal products approved for novel therapies within the meaning of Section 4, paragraph 9 Medicinal Products Act, there is an obligation to submit evidence in accordance with Section 35a, paragraph 1b SGB V. Medical treatment with such a medicinal product is not subject to the assessment of examination and treatment methods according to Sections 135, 137c or 137h.

For medicinal products for the treatment of rare diseases (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to Section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V). Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a paragraph 1, sentence 3, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds € 50 million in the last 12 calendar months. According to Section 35a paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, subsection 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5 Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a paragraph 1 sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation the G-BA modified the procedure for the benefit assessment of orphan drugs at its session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be

assumed by law. Rather, the extent of the additional benefit is assessed exclusively on the basis of the marketing authorisation studies by the G-BA indicating the significance of the evidence.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a, paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the legal limit of € 50 million and is therefore subject to an unrestricted benefit assessment (cf. Section 35a, paragraph 1, sentence 12 SGB V). According to Section 35a paragraph 2 SGB V, the assessment by the G-BA must be completed within three months of the relevant date for submission of the evidence and published on the internet.

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

2. Key points of the resolution

The relevant date for the first placing on the (German) market of the active ingredient idecabtagen vicleucel in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 January 2022. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 29 December 2021.

Idecabtagen vicleucel indicated for the treatment of multiple myeloma is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. Idecabtagen vicleucel is a gene therapeutic within the meaning of Section 4, paragraph 9 Medicinal Products Act.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the marketing authorisation studies by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 1 April 2022 together

with the IQWiG assessment on the website of the G-BA (http://www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA has adopted its resolution on the basis of the dossier of the pharmaceutical company, the dossier assessment carried out by the G-BA, the assessment of treatment costs and patient numbers (G22-01) prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure.

In order to determine the extent of the additional benefit, the G-BA has assessed the studies relevant for the marketing authorisation considering their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7, sentence 1, numbers 1 – 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of idecabtagen vicleucel.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Idecabtagen vicleucel (Abecma) according to the product information

Abecma is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.

Therapeutic indication of the resolution (resolution of 16 June 2022):

see the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

Adults with relapsed and refractory multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.

In summary, the additional benefit of idecabtagen vicleucel is assessed as follows:

Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

Justification:

To assess the additional benefit of idecabtagen vicleucel (Ide-Cel), the pharmaceutical company submitted data from the single-arm marketing authorisation-related CRB-401 and

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

KarMMa studies. In addition, the pharmaceutical company conducts various indirect comparisons without a bridge comparator on efficacy and safety endpoints in the dossier.

In the pivotal studies, different doses of Ide-Cel were investigated. In the dossier, the pharmaceutical company evaluates the respective sub-population of subjects who were treated with the dose of 260 - 500 x 10^6 CAR+ T cells in accordance with the marketing authorisation. The respective assessment-relevant sub-population of the CRB-401 and KarMMa studies submitted by the pharmaceutical company is used for the benefit assessment.

KarMMa study

The ongoing KarMMa study is an open-label, single-arm phase II study that enrolled subjects with multiple myeloma who had received at least three prior treatment regimens including a proteasome inhibitor (PI), immunomodulatory agent (IMiD) and a CD38 antibody and were refractory to the last therapy. For each prior therapy, at least two cycles of treatment had to have been administered, unless the best response corresponded to a progressive disease. In addition, subjects had to have an ECOG performance status (PS) of 0 to 1. Patients with central nervous system (CNS) involvement were excluded from study participation.

The intervention in the KarMMa study consisted of three phases. Initially, mononuclear cells were obtained from the peripheral blood of the subjects by means of leukapheresis, from which the patient-individual production of Ide-Cel was subsequently carried out. Leukapheresis was done about four to five weeks before the planned infusion of Ide-Cel. Bridge therapy until completion of Ide-Cel could be given for disease control up to 14 days prior to administration of lymphodepleting chemotherapy (LDC) according to the assessment of the medical investigators. Bridge therapy could include corticosteroids, alkylants, IMiD, PI and/or CD38 antibodies as monotherapy or in combination. Five days before the infusion of Ide-Cel, LDC was carried out administering fludarabine and cyclophosphamide for three consecutive days. From the day of Ide-Cel infusion, subjects were hospitalised for up to 14 days after Ide-Cel infusion for monitoring and management of cytokine release syndrome (CRS) and neurotoxicity.

Of the 140 subjects included, 136 patients were scheduled to receive a dose of Ide-Cel that was compliant with the marketing authorisation. Of these, 124 subjects received an infusion with Ide-Cel (~91%). Re-therapy with Ide-Cel could take place under specific conditions (e.g., at least eight weeks since the first infusion, evidence of disease progression, etc.) and was carried out in 31 patients.

Follow-up was for at least 24 months. After completion of the KarMMa study, subjects were required to participate in the long-term follow-up study GC-LTFU-001, in which the long-term side effects were monitored for up to 15 years.

The study is being conducted in 20 study sites across North America and Europe. Enrolment took place between 2017 and 2018. The primary endpoint is the overall response rate (at least achievement of a partial response). Secondary endpoints include overall survival, endpoints

on morbidity and health-related quality of life, and side effects. The fourth data cut-off of the study, which was conducted 24 months after the first infusion of the last test subject with Ide-Cel, is used for the benefit assessment.

CRB-401 study

The ongoing CRB-401 supportive study is a two-part, non-randomised phase I study in subjects with relapsed and refractory multiple myeloma. The study consists of a dose escalation phase (part A) and a dose expansion phase (part B).

Part A included patients who had received at least three prior lines of therapy including a PI and an IMiD or were double-refractory to a PI and an IMiD. For enrolment in study part B, subjects had to have received prior therapy with a PI, an IMiD and daratumumab and be refractory to the last treatment. Analogous to the KarMMa study, the subjects also had to have an ECOG-PS of 0 to 1 and no CNS involvement for both study phases.

The intervention carried out and the prerequisites for re-therapy with Ide-Cel corresponded as far as possible to the procedure in the KarMMa study. With regard to the choice of bridge therapy, there were initially no limitations in the CRB-401 study. A total of 67 subjects were enrolled in the study. A total of 42 patients were envisaged for dosing in compliance with the marketing authorisation. Of these, 38 subjects received an infusion with Ide-Cel (~90%). Re-therapy with Ide-Cel was carried out in 18 patients.

Follow-up in the CRB-401 study was for a maximum of 60 months at the start or until disease progression, whichever came first. Protocol amendment 5.0 stipulated those patients who experienced disease progression should also be followed up for at least 6 months. After completion of the CRB-401 study, patients were required to participate in the long-term follow-up study LTF-305, which was later bundled into the GC-LTFU-001 study.

The data in the dossier does not clearly indicate the number of subjects who were not followed up in the CRB-401 study or the long-term follow-up studies due to disease progression. The information provided by the pharmaceutical company in the written statement procedure shows that no follow-up was carried out for 12 subjects (about 29%).

Primary endpoints of the study are the incidence of adverse events (AEs) and laboratory parameters as well as dose-limiting toxicity. The study is being conducted in nine study sites in the U.S. Enrolment took place between 2015 and 2019. The third data cut-off of the study of 7 April 2020 was used for the benefit assessment.

On the indirect comparisons presented

Indirect comparisons on efficacy

For the efficacy endpoints in the dossier, the pharmaceutical company makes indirect comparisons without a bridge comparator of the KarMMa and CRB-401 studies with the NDS-MM-003, PREAMBLE and OPTIMISMM (MM-007) studies, and justifies this procedure with the availability of patient-individual data for the studies mentioned. The indirect comparisons

mainly refer to the endpoint of overall survival. In addition, the pharmaceutical company compares endpoints on symptomatology between the KarMMa and PREAMBLE studies.

The indirect comparisons to the CRB-401 study are not considered further in this benefit assessment, as the estimator for the endpoint of overall survival of the CRB-401 study is not considered valid. In this regard, reference is made to the comments below on the endpoint category "mortality".

For the selection of confounders, the pharmaceutical company has chosen a two-step procedure. In the first step, comparator cohorts were selected from reference studies using inclusion and exclusion criteria based on those of the Ide-Cel studies. In the second step, relevant confounders in the present therapeutic indication were identified via a systematic literature research and interviews with clinical experts. All identified confounders with sufficient data availability in the studies were adjusted using propensity score methods. The systematic literature research was limited by the pharmaceutical company to indirect comparisons and observational studies were explicitly excluded as a source for the identification of confounders. Based on the adjusted indirect comparisons identified in this research, the pharmaceutical company compiled a list of all confounders used in the adjusted indirect comparisons.

The pharmaceutical company's approach is considered adequate in principle, but is limited in that only confounders with data availability in the underlying studies of the adjusted indirect comparisons are identified. Overall, uncertainties remain as to whether all relevant confounders for the present specific treatment setting of relapsed and refractory multiple myeloma after at least three prior therapies could be identified in the systematic literature research and the expert interviews. In addition, confounders were not included in the propensity score model for more than 30% missing data.

NDS-MM-003 study versus KarMMa study

The NDS-MM-003 study is a retrospective cohort study collecting data from adults with relapsed and refractory multiple myeloma who have received at least three prior therapies, including an IMiD, a PI and an anti-CD38 antibody. For the indirect comparison with the KarMMa study, a prespecified study protocol, a statistical analysis plan and a study report are available, as well as specifically, a study protocol and statistical analysis plan for the requirements of the early benefit assessment according to Section 35a SGB V.

Enrolment in the retrospective cohort study was between November 2015 and September 2018. Data were collected from clinical study sites and research databases (e.g., Flatiron). Due to overlapping enrolment periods, there are overlaps in the enrolment of subjects in the KarMMa and NDS-MM-003 studies. According to the written statement of the pharmaceutical company, this applies to 14 out of 136 subjects (~10%) of the KarMMa study and 44 out of 190 persons (~23%) of the NDS-MM-003 study. Subjects who had already received BCMA-targeted therapy or gene therapy were explicitly excluded from the cohort of the NDS-MM-003 study. Overall, in the present case, the uncertainty resulting from the potential risk of bias

due to the overlap of the study periods is considered insignificant due to the low number of subjects concerned.

The pharmaceutical company uses the subjects in the NDS-MM-003 cohort to form an ERRMM cohort ("eligible relapsed refractory multiple myeloma" cohort), whose inclusion and exclusion criteria largely correspond to those of the Ide-Cel study. However, morbidity-oriented exclusion criteria were only applied if data were available for the respective criterion. Information on the number of subjects for whom no data on these morbidity-specific criteria were available is not available.

For the indirect comparison, the pharmaceutical company takes 13 confounders into account. However, as confounders with > 30% missing data were not included, clinically relevant confounders such as the presence of an extramedullary plasmacytoma, the cytogenetic risk profile, the ECOG-PS, focal lesions and bone lesions, creatinine clearance and others were not considered in the analyses. The clinical relevance of the characteristics "presence of an extramedullary plasmacytoma" and "cytogenetic risk profile" in particular was also explained by the scientific-medical society during the oral hearing of the present benefit assessment procedure. Based on the available characteristics of the sub-population of the KarMMa study and the cohort study NDS-MM-003 that is compliant with the marketing authorisation, the structural equality of the patient populations cannot be assessed with sufficient certainty with regard to the clinically relevant confounders that were not taken into account. For example, about 50% of the subjects in the KarMMa study did not have a high cytogenetic risk and about 59% did not have extramedullary plasmacytoma. In the cohort study NDS-MM-003, no information is available for these characteristics for more than 50% and 60% of the subjects, respectively. Also, for other factors such as creatinine clearance and ECOG-PS, the comparability between the studies cannot be assessed due to the high percentage of > 40% missing values.

PREAMBLE study versus KarMMa study

The PREAMBLE study is a multicentre prospective cohort study that has been collecting data from the day-to-day care of subjects with multiple myeloma since 2012. Patients who were refractory to the last line of therapy and received treatment with an IMiD, a PI or a novel treatment regimen were enrolled. The subjects were enrolled in different study sites (university hospitals, research centres and doctors' practices) and followed up for three years. A prespecified study protocol and a statistical analysis plan are available for the assessment and analysis of data from the PREAMBLE study, but not for the indirect comparison with the KarMMa study.

Analogous to the procedure for the NDS-MM-003 study, the pharmaceutical company applies the inclusion and exclusion criteria of the Ide-Cel study to the patient population of the PREAMBLE study and forms an ERRMM cohort from this. However, due to data availability, the pharmaceutical company only takes into account a part of the inclusion and exclusion criteria, whereby morbidity-specific aspects in particular were not included.

For the indirect comparison, the pharmaceutical company takes 11 confounders into account. Since confounders with > 30% missing data were also not used in the present indirect comparison, clinically relevant confounders such as the presence of an extramedullary plasmacytoma, the cytogenetic risk profile, the ECOG-PS, focal lesions and bone lesions, creatinine clearance and others were not taken into account in the analyses.

The structural equality of the patient populations with regard to clinically relevant confounders can therefore also not be assessed with sufficient certainty for this indirect comparison. For the PREAMBLE study, for example, no data are available for the characteristic "presence of an extramedullary plasmacytoma" and values of about 80% of the subjects are missing for the characteristic "cytogenetic risk profile".

In the PREAMBLE study, patient-reported endpoints on morbidity and health-related quality of life were also collected every 3 months in the first year and every 6 months in the second and third years. However, since the return rates related to the relevant ERRMM cohort were a maximum of 19% at a relevant survey time point, these results are not considered further in the present benefit assessment.

MM-007 study versus KarMMa study

The MM-007 study is an open-label, randomised controlled trial comparing pomalidomide + bortezomib + dexamethasone versus bortezomib + dexamethasone. Adults with multiple myeloma after one to three prior therapies, which had to include at least two consecutive cycles of lenalidomide, were enrolled in the study. Subjects also had to have disease progression during or after the last pretreatment. No statistical analysis plan and study protocol are available for the indirect comparison with the KarMMa study.

The pharmaceutical company shall form an ERRMM cohort from the patient population of the MM-007 study according to the following criteria: received at least three prior therapies, completed at least two consecutive treatment cycles for each treatment regimen, received at least one IMiD, PI and CD38 antibody, received at least one subsequent myeloma therapy, refractoriness to the last therapy. As these criteria did not apply to a sufficient number of people at baseline of the study, subjects who only fulfilled the criteria mentioned in the course of the follow-up phase of the study were also included in the ERRMM cohort. Thus, a total of 41 subjects were included in the ERRMM cohort. The index time point for patients who only met the inclusion criteria in the follow-up phase does not correspond to the baseline value of the MM-007 study, but to the time point of initiation of the subsequent therapy. According to the information provided by the pharmaceutical company, only the confounders age, gender, number of previous lines of therapy and time since diagnosis could be considered in the model. For all other clinically relevant confounders identified, neither an adjustment nor a matching of patient characteristics could be performed. Accordingly, the structural equality for clinically relevant confounders cannot be assessed with sufficient certainty for the present indirect comparison either.

Conclusion on the indirect comparisons on efficacy

Overall, it cannot be assumed with sufficient certainty that the relevant patient cohorts of the NDS-MM-003, PREAMBLE and MM-007 studies are structurally identical to the patient population of the KarMMa study. The patients enrolled in the KarMMa study are intensely pretreated, had received a broad spectrum of available therapies as well as a large number of prior therapies, and accordingly have a high percentage of double and triple-refractory subjects. However, due to the specified inclusion and exclusion criteria, the KarMMa study included relatively young subjects (median = 61 years) in good health status. The patient characteristics of the KarMMa study with regard to the presence of an extramedullary plasmacytoma, cytogenetic risk and tumour burden also do not provide sufficient evidence for a very poor prognosis of the enrolled subjects. Due to the high percentage of missing values, no adjustment or matching of the patient populations to the confounders identified as relevant in the confounder selection, in particular to the characteristics of presence of an extramedullary plasmacytoma and cytogenetic risk, could be performed. Thus, the indirect comparisons presented are subject to considerable uncertainties. Furthermore, the results do not indicate an effect on an order of magnitude, where it can be assumed with sufficient certainty that the observed differences are not due to systematic risk of bias alone. As a result, the submitted indirect comparisons on the efficacy endpoints are not used for the present benefit assessment.

Indirect comparisons for safety

For the endpoint category of side effects, the pharmaceutical company presents descriptive comparisons of the study arms of the KarMMa and CRB-401 studies versus the study arms of the phase III MM-007, MM-003 and ELOQUENT-3 studies. These are non-adjusted comparisons of incidence rates of adverse events (AEs) without calculation of effect estimators.

With regard to the characteristics of the MM-007 study, reference is made to the explanations above. The MM-003 study is a randomised, open-label, phase III study comparing pomalidomide + low-dose dexamethasone versus high-dose dexamethasone in adults with relapsed or refractory multiple myeloma, with at least two prior therapies, including lenalidomide and bortezomib. The ELOQUENT-3 study is a randomised, multicentre, phase II study comparing elotuzumab + pomalidomide + dexamethasone versus pomalidomide + dexamethasone. Adults with relapsed or refractory multiple myeloma who failed therapy with lenalidomide and a PI were enrolled in the study.

All subjects included in the KarMMa and CRB-401 studies were used for the evaluation. The patient cohort relevant for the indirect comparison was selected exclusively on the basis of the characteristic "treatment with at least three prior treatment regimens". However, on the basis of this characteristic alone, a sufficient structural equality of the patient populations cannot be assumed, as there are different inclusion and exclusion criteria between the studies as well as differences in the baseline characteristics. In principle, indirect comparisons without

a bridge comparator based on non-structurally identical cohorts without adequate adjustment via the consideration of relevant confounders and without the calculation of effect estimators are considered inadequate. Therefore, the submitted indirect comparisons on side effects are not used for the present benefit assessment.

On the results of the KarMMa and CRB-401 studies by endpoint:

Mortality

The overall survival is defined in the CRB-401 study as the time from randomisation to death from any cause. For the benefit assessment, the operationalisation as time from leukapheresis to death from any cause was evaluated as the primary analysis. For overall survival, the data of the long-term follow-up studies were taken into account as stated by the pharmaceutical company.

In the KarMMa study, follow-up of overall survival of non-infused subjects was for 30 days. In case of disease progression, follow-up was planned for up to 24 months. The median survival time for the KarMMa study is 23.3 months. Due to the single-arm study design, a comparative assessment of the results on overall survival is not possible.

In contrast, in the CRB-401 study, follow-up of subjects with disease progression was only introduced with amendment 5.0. As described above, 28.6% of subjects were not followed up for overall survival due to disease progression. In the dossier, the pharmaceutical company states that the median follow-up duration of the CRB-401 study is 11.5 months. In its written statement, the pharmaceutical company states that the follow-up of the long-term follow-up studies was not included. Including the long-term follow-up studies, the median follow-up duration is about 18 months. Even taking into account the corrected median follow-up duration, this is relatively short in relation to the median survival time (about 35 months). Together with the high number of censored subjects (about 70%), the estimator for overall survival of the CRB-401 study is still considered invalid and therefore not considered for the present benefit assessment.

Morbidity

Progression-free survival

Progression-free survival (PFS) was assessed using the International Myeloma Working Group (IMWG) criteria according to Kumar et al (2016), based on laboratory parameters as well as haematological and imaging methods. For the benefit assessment, the evaluation at the time from leukapheresis to documented disease progression or death from any cause is used.

The median PFS of the KarMMa study was 9.1 months and of the CRB-401 study 9.9 months.

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. The “Mortality” endpoint component is already assessed via the “overall survival” secondary endpoint as an independent endpoint. The morbidity component "disease

progression" was assessed according to IMWG criteria and thus, not in a symptom-related manner but by means of laboratory parametric, imaging, and haematological procedures. Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient relevance of the endpoint PFS.

Due to the single-arm study design, a comparative assessment of the results on PFS is not possible.

Health status (EQ-5D VAS)

Health status was only assessed in the KarMMa study using the visual analogue scale (VAS). The pharmaceutical company presents evaluations on response criteria ≥ 7 points, ≥ 10 points, and 15% of the scale range (0-100). Only subjects who were treated with Ide-Cel and had a baseline and post-baseline assessment (PRO analysis kit) are included in the evaluation of the change in EQ-5D VAS. Assessments of subjects who received re-therapy with Ide-Cel were not included in the evaluations. Restricting the patient population to those who have received Ide-Cel infusion is viewed critically, as leukapheresis, waiting time for product to be prepared and lymphocyte-depleting chemotherapy are inherent components of treatment with Ide-Cel. The influence of all components of the therapy with Ide-Cel on the treatment of patients can only be assessed by looking at all subjects from leukapheresis onwards. Furthermore, the exclusion of subjects who had no further assessment after baseline is also not comprehensible. The PRO analysis kit differs by fourteen subjects (~10%) from the assessment-relevant patient population for whom leukapheresis was performed (N = 136).

The return rates are calculated by the pharmaceutical company in the dossier only on the basis of the Ide-Cel-treated subjects. Looking at the entire PRO analysis kit, the return rate at month 3 is merely 67%. Looking at Ide-Cel treated subjects who are still alive and participating in the study, the return rate at month 3 is about 74%. Return rates related to all subjects who received leukapheresis and are still alive are provided by the pharmaceutical company neither in the dossier nor in its written statement.

The return rate can therefore not be adequately assessed. In addition, no evaluations are available for the relevant patient population that received leukapheresis. Thus, patients who experienced disease progression after leukapheresis and before Ide-Cel infusion or who discontinued the study before Ide-Cel infusion are not included in the evaluations presented. The data on the EQ-5D VAS are therefore not considered usable for the present benefit assessment. Notwithstanding this, due to the single-arm study design, a comparative assessment of the data on the EQ-5D VAS is not possible.

Symptomatology

Disease symptomatology was assessed exclusively in the KarMMa study using the symptom scales of the EORTC-QLQ-C30 questionnaire and the myeloma-specific additional module EORTC-QLQ-MY20. In the dossier, the pharmaceutical company submits evaluations on the percentage of subjects with a change in the scale score of ≥ 10 points compared to screening.

The evaluations on symptomatology are based on the PRO-analysis kit. Return rates are also calculated by the pharmaceutical company exclusively on the basis of the Ide-Cel treated patient population. Regarding the uncertain assessment of the return rates and the assessment of the patient population used for the evaluation, please refer to the comments on the endpoint EQ-5D VAS.

An assessment of the return rates related to all subjects who received leukapheresis and are still alive is not possible. In addition, no evaluations are available for the relevant patient population that received leukapheresis. Thus, patients who experienced disease progression after leukapheresis and before Ide-Cel infusion or who discontinued the study before Ide-Cel infusion are not included in the evaluations presented. Therefore, the evaluations of the symptom scales of the EORTC-QLQ-C30 questionnaire and the myeloma-specific additional module EORTC-QLQ-MY20 are not considered usable for the present benefit assessment. Nevertheless, a comparative assessment of the data on the EORTC QLQ-C30 and -MY20 is not possible due to the single-arm study design.

Quality of life

Health-related quality of life was assessed exclusively in the KarMMa study using the functional scales of the EORTC-QLQ-C30 questionnaire and the myeloma-specific additional module EORTC-QLQ-MY20. In the dossier, the pharmaceutical company submits evaluations on the percentage of subjects with a change in the scale score of ≥ 10 points compared to screening.

The evaluations on health-related quality of life are based on the PRO-analysis kit. Return rates are also calculated by the pharmaceutical company exclusively on the basis of the Ide-Cel treated patient population. Regarding the uncertain assessment of the return rates and the assessment of the patient population used for the evaluation, please refer to the comments on the endpoint EQ-5D VAS.

An assessment of the return rates related to all subjects who received leukapheresis and are still alive is not possible. In addition, no evaluations are available for the relevant patient population that received leukapheresis. Thus, patients who experienced disease progression after leukapheresis and before Ide-Cel infusion or who discontinued the study before Ide-Cel infusion are not included in the evaluations presented. Therefore, the evaluations of the functional scales of the EORTC-QLQ-C30 questionnaire and the myeloma-specific additional module EORTC-QLQ-MY20 are not considered usable for the present benefit assessment. Nevertheless, a comparative assessment of the data on the EORTC QLQ-C30 and -MY20 is not possible due to the single-arm study design.

Side effects

The assessment of the endpoints on side effects differs depending on the study phase of the KarMMa and CRB-401 studies.

In the KarMMa study, only any intervention-related adverse events (AEs) and serious AEs (SAEs) were recorded until LDC. From LDC to month 6 after infusion with Ide-Cel, a complete recording of side effects was made. From month 6 to month 24, AEs with CTCAE grade ≥ 3, SAEs and AEs of special interest (AESI) were recorded, and from month 24 onwards only the above-mentioned AE categories were recorded, whereby the AEs also had to be related to the study medication.

In the CRB-401 study, all AEs were collected completely up to month 24 after infusion with Ide-Cel, but at the start only up to the time of disease progression or study discontinuation. Amendment 5.0 specified that all subjects should be followed up for AEs for at least 6 months from Ide-Cel infusion in the event of disease progression. After month 24, AEs with CTCAE grade ≥ 3, SAEs and AESI were documented.

In addition, all AEs related to the study medication should be collected in the long-term follow-up studies LTF-305 and GC-LTFU-001. The data of the long-term follow-up studies were considered in the dossier according to the explanations of the pharmaceutical company.

SAEs occurred primarily in the treatment phase between Ide-Cel infusion and the end of follow-up in about 70% and 76% of subjects, respectively. Severe AEs were present in approximately 30% and 35% of subjects, respectively, in the phase between leukapheresis and LDC, in approximately 54% and 65% of subjects, respectively, in the phase between LDC and Ide-Cel infusion, and in >97% of subjects in the phase between Ide-Cel infusion to end of follow-up.

In terms of AESI, cytokine release syndrome (CRS) occurred in 84% and 92% of patients in the phase from Ide-Cel infusion. CRS was categorised as grade 1 or 2 in > 75% of subjects. Neurological toxicity (broad) occurred primarily in the therapy phase after Ide-Cel infusion in about 70% and 86% of patients, respectively. In terms of focused neurotoxicity, which was present in approximately 41% and 52% of subjects after Ide-Cel infusion, the events were predominantly classified as grade 1 and 2.

Due to the single-arm study design, a comparative assessment of the data on side effects is not possible.

Overall assessment

The present benefit assessment is based on the results of the pivotal phase II KarMMa study on mortality, morbidity, health-related quality of life and side effects. In addition, the data of the supportive phase I CRB-401 study on mortality and side effects are available.

Due to the single-arm study design, a comparative assessment of the data on idecabtagen vicleucel is not possible.

The indirect comparisons of efficacy endpoints of the KarMMa study with the NDS-MM-003, PREAMBLE and MM-007 studies are subject to considerable uncertainty, mainly due to clinically relevant confounders that were not taken into account. A lack of structural equality of the patient populations cannot be ruled out. Taking into account these uncertainties, the effect estimator for overall survival is not in an order of magnitude to derive an effect with sufficient confidence. The indirect comparisons on symptomatology (PREAMBLE versus KarMMa) were not considered in the present benefit assessment due to the low return rates in the PREAMBLE study. In addition, the indirect comparisons for overall survival to the CRB-401 study were not included due to the estimator for median survival being invalid.

The indirect comparisons on endpoints of side effects are not used for the present benefit assessment. Indirect comparisons without a bridge comparator based on cohorts that are not structurally identical without adequate adjustment via the consideration of relevant confounders and without the calculation of effect estimators are considered unsuitable for the benefit assessment.

Overall, the indirect comparisons presented are unsuitable for deriving statements about the extent of the additional benefit.

In the overall assessment, the extent of the additional benefit is classified as non-quantifiable since the scientific data does not allow quantification.

Significance of the evidence

The present benefit assessment is based on the data from the pivotal, single-arm KarMMa study and the supportive, single-arm CRB-401 study. There is no adequate comparison.

Since only single-arm data are available and a comparative assessment is not possible, the reliability of data is assessed with a hint.

In the overall assessment, the result is a hint for a non-quantifiable additional benefit concerning the significance of the evidence.

2.1.3 Summary of the assessment

The present benefit assessment concerns the benefit assessment of the new medicinal product Abecma® with the active ingredient idecabtagen vicleucel.

Abecma® has received conditional marketing authorisation and was approved as an orphan drug for the treatment of relapsed and refractory multiple myeloma in adults who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody, and have demonstrated disease progression on the last therapy.

For the benefit assessment, the data of the pivotal, single-arm KarMMa study and the supportive CRB-401 study on mortality, morbidity, quality of life and side effects were presented.

For the indirect comparisons carried out on efficacy endpoints, a lack of structural equality of the patient populations cannot be ruled out. Due to a lack of data, clinically relevant confounders were not included. Taking into account these significant uncertainties, the effect estimator for overall survival is also not in an order of magnitude to derive an effect with sufficient confidence.

The indirect comparisons on endpoints of side effects without a bridge comparator based on non-structurally identical cohorts without adequate adjustment via the consideration of relevant confounders and without the calculation of effect estimators are considered unsuitable for the benefit assessment.

On the basis of the indirect comparisons presented, it is therefore not possible to make a statement about the extent of the additional benefit.

Since only single-arm data are available and a comparative assessment is not possible, the reliability of data is assessed with a hint.

In the overall assessment, a hint for a non-quantifiable additional benefit is identified for Abecma® since the scientific data does not allow quantification.

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

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

The pharmaceutical company calculated the number of patients in the SHI target population using five derivation steps.

These are subject to uncertainties due to the following aspects:

- The determination of the target population solely on the basis of incidence reports leads to uncertainties, since the percentages of newly ill subjects are transferred to subjects ill in previous years. This uncertainty also applies to the determination of the percentage values for subjects with smouldering multiple myeloma (SMM) and disease progression from an incident population.
- The percentage value of multiple myeloma in all diagnoses summarised under ICD-10 C90.- of 73.4% results from a significantly lower percentage value of 48% - 62% of the North Rhine-Westphalian cancer registry in relation to the data of other cancer registries. The percentage value in the data of the other cancer registries is over 90% in each case. The assumed percentage value is therefore potentially underestimated.
- When calculating the percentage of people with multiple myeloma and at least three prior therapies including an immunomodulatory agent, proteasome inhibitor and CD38 antibody, only subjects who were receiving causal therapy at the time of observation are considered. On the basis of the submitted calculation, it cannot be checked whether a

complete and correct coverage of all active ingredients approved for the therapeutic indication was carried out. The calculated percentage value does not take into account subjects with a prior therapy who received a fourth line of therapy in the same year. It also remains open whether subjects who were not assigned to any further therapy after the fourth line of therapy are eligible for the medicinal product to be assessed.

Taking into account the procedure for belantamab mafodotin (multiple myeloma after at least 4 prior therapies, resolution of 4 March 2021) and the described uncertainties of the current calculation for idecabtagen vicleucel, the following percentage values are assumed for a best possible estimate of the target population[2]:

- Current 10-year prevalence of multiple myeloma: 32,200
- Percentage of subjects with multiple myeloma in diagnosis group ICD-10 C90.-: 97.3%
- Percentage of subjects with multiple myeloma requiring treatment: 85.6% - 92%
- Percentage of subjects with at least 3 prior therapies: 5.2%
- Percentage of SHI-insured subjects: 88.1%

This results in about 1,200 to 1,300 subjects in the SHI target population.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Abecma (active ingredient: idecabtagen vicleucel) at the following publicly accessible link (last access: 2 May 2022):

https://www.ema.europa.eu/en/documents/product-information/abecma-epar-product-information_en.pdf

This medicinal product was authorised under “special conditions”. This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material and a patient emergency card. Training material for all healthcare professionals who will prescribe, dispense, and administer idecabtagen vicleucel includes instructions for identifying, treating, and monitoring cytokine release syndrome and neurological side effects. It also includes instructions on the cell thawing process, availability of 1 dose of tocilizumab at the point of

[2] IQWiG report no. 1320; idecabtagen vicleucel (multiple myeloma); G22-01; 29.03.2022

treatment, provision of relevant information to patients, and full and appropriate reporting of side effects.

The patient training programme should explain the risks of cytokine release syndrome and serious neurologic side effects, the need to report symptoms immediately to the treating physician, to remain close to the treatment facility for at least 4 weeks after infusion of idecabtagen vicleucel, and to carry the patient emergency card at all times.

Idecabtagen vicleucel must be used in a qualified treatment centre. For the infusion of idecabtagen vicleucel in multiple myeloma diagnosed with C90.00 and C90.01, the quality assurance measures for the use of CAR-T cells in B-cell neoplasms apply (ATMP Quality Assurance Guideline, Annex 1).

There is limited experience of re-treatment of patients with a second dose of Abecma. The response to re-treatment with Abecma was irregular and of shorter duration compared to the first treatment. In addition, fatal courses were observed in patients who were retreated.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 June 2022).

Idecabtagen vicleucel is listed on LAUER-TAXE®, but is only dispensed to appropriate qualified inpatient treatment facilities. Accordingly, the active ingredient is not subject to the Pharmaceutical Price Ordinance (Arzneimittelpreisverordnung) and no rebates according to Section 30 or Section 130a SGB V apply. The calculation is based on the sales price of the pharmaceutical company, in deviation from the usually taken into account data of the LAUER-TAXE®.

Idecabtagen vicleucel is administered as a single intravenous infusion according to the information provided in the product information.

Idecabtagen vicleucel are autologous T cells genetically modified to express a chimeric antigen receptor directed against BCMA (B-cell maturation antigen). Accordingly, the concentration of viable CAR+ T cells may vary between patient-specific batches. One or more infusion bags contain a total of 260 x 10^6 to 500 x 10^6 viable CAR+ T cells.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Idecabtagen vicleucel	Single dose	1	1	1

Consumption:

In the following, the consumption of infusion bags is shown according to the information in the product information. These are administered to the patient in a single infusion depending on the number of cells per infusion bag. The annual treatment costs of idecabtagen vicleucel are independent of the specific number of infusion bags used.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Idecabtagen vicleucel	260 x 10^6 - 500 x 10^6 viable CAR+ T cells	260 x 10^6 - 500 x 10^6 viable CAR+ T cells	1 or more infusion sachets	1	1 or more infusion sachets

Costs:

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (sales price of the pharmaceutical company)	Value-added tax	Costs
Medicinal product to be assessed				
Idecabtagen vicleucel	1 or more infusion bags (260 x 10^6 - 500 x 10^6 viable CAR+ T cells)	€ 350,000.00	€ 0	€ 350,000.00

Costs for additionally required SHI services:

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

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

Idecabtagen vicleucel is an autologous cell product produced from the patient's own T cells. A leukapheresis is usually necessary to obtain the cell material. Since leukapheresis is part of the manufacture of the medicinal product pursuant to Section 4 paragraph 14 Medicinal Products Act, no further costs are incurred in this respect for the medicinal product to be assessed.

Lymphocyte depletion

According to the product information of idecabtagen vicleucel, lymphocyte-depleting chemotherapy should be administered before the CAR-T cells are administered. To this end, cyclophosphamide (daily 300 mg/m^2 intravenously for 3 days) and fludarabine (daily 30 mg/m^2 intravenously for 3 days) should be administered. For dosages depending on body weight or body surface area (BSA), the average body measurements from the official representative statistics “Microcensus 2017 – body measurements of the population” were applied (average body height: 1.72 m; average body weight: 77 kg). This results in a body surface area of 1.90 m^2 (calculated according to Du Bois 1916).

Type of service	Cost per pack	Costs after deduction of statutory rebates[3,4]	Costs per service	Treatment days per year	Costs/ patient/ year
Medicinal product to be assessed					
Idecabtagen vicleucel					
Lymphocyte depleting chemotherapy					
Cyclophosphamide (300 mg/m^2, IV)	€ 61.21 - 10 x 200 mg	€ 56.67 (€ 1.77, € 2.77)	€ 17.00	3	€ 56.67
Fludarabine (30 mg/m^2, IV)	€ 118.50 - 1 x 50 mg	€ 111.64 (€ 1.77, € 5.09)	€ 223.28	3	€ 669.84

LAUER-TAXE® last revised: 1 June 2022

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 81 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

[3] Rebate according to Section 130 SGB V
[4] Rebate according to Section 130a SGB V

3. Bureaucratic costs calculation

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

4. Process sequence

On 29 December 2021, the pharmaceutical company submitted a dossier for the benefit assessment of idecabtagen vicleucel to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 1 April 2022 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 22 April 2022.

The oral hearing was held on 9 May 2022.

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

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 8 June 2022, and the proposed resolution was approved.

At its session on 16 June 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	29 March 2022	Information of the benefit assessment of the G-BA
Working group Section 35a	4 May 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	9 May 2022	Conduct of the oral hearing
Working group Section 35a	18 May 2022 1 June 2022	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee Medicinal products	8 June 2022	Concluding discussion of the draft resolution
Plenum	16 June 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 16 June 2022

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken