Idecabtagene vicleucel (multiple myeloma, ≥ 2 prior therapies)

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

EXTRACT

Project: A24-35 Version: 1.0 Status: 27 Jun 2024 DOI: 10.60584/A24-35_en

[1] Translation of Sections I 1 to I 6 of the dossier assessment *Idecabtagen vicleucel (multiples Myelom, ≥ 2 Vortherapien) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Idecabtagene vicleucel (multiple myeloma, ≥ 2 prior therapies) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

2 April 2024

Internal Project No.

A24-35

DOI-URL

https://doi.org/10.60584/A24-35_en

Address of publisher

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

- Helmut Ostermann, LMU Klinikum

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 the plasmacytoma/multiple myeloma support group NRW (Plasmozytom/Multiples Myelom NRW) for participating in the written exchange and for their support. The respondent and the plasmacytoma/multiple myeloma support group NRW were not involved in the actual preparation of the dossier assessment.

IQWiG employees involved in the dossier assessment

- Can Ünal
- Anna-Katharina Barnert
- Tobias Effertz
- Reza Fathollah-Nejad
- Simone Heß
- Philip Kranz
- Sabine Ostlender
- Anke Schulz

Keywords

Idecabtagene Vicleucel, Multiple Myeloma, Benefit Assessment, NCT03651128

Part I: Benefit assessment

I Table of contents

Page

I List of tables[2]

Page

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

I List of figures

Page

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
DPd	daratumumab in combination with pomalidomide and dexamethasone
DVd	daratumumab in combination with bortezomib and dexamethasone
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EORTC QLQ-MY20	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Multiple Myeloma Module 20
EPAR	European Public Assessment Report
EPd	elotuzumab in combination with pomalidomide and dexamethasone
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IMWG	International Myeloma Working Group
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IRC	Independent Response Committee
IRd	ixazomib in combination with lenalidomide and dexamethasone
Kd	carfilzomib in combination with dexamethasone
PFS	progression-free survival
PRO-SAP	statistical analysis plan for patient-reported outcomes
RCT	randomized controlled trial
SAE	serious adverse event
SAP	statistical analysis plan
SGB	Sozialgesetzbuch (Social Code Book)
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) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug idecabtagene vicleucel. 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 2 April 2024.

Research question

The aim of this report is to assess the added benefit of idecabtagene vicleucel compared with the appropriate comparator therapy (ACT) in adult patients with relapsed and refractory multiple myeloma who have received at least 2 prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-cluster of differentiation (CD)38 antibody and have demonstrated disease progression on the last therapy.

The research questions shown in Table 2 result from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of idecabtagene vicleucel (multipage table)

Research question	Therapeutic indication	ACT[a]
1	Adults with relapsed and refractory multiple myeloma who have received 2 to 3 prior therapies and have demonstrated disease progression on the last therapy; pretreatment includes an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody	Individualized treatment[b] selected from: ▪ carfilzomib in combination with lenalidomide and dexamethasone ▪ elotuzumab in combination with lenalidomide and dexamethasone ▪ elotuzumab in combination with pomalidomide and dexamethasone ▪ daratumumab in combination with bortezomib and dexamethasone ▪ daratumumab in combination with lenalidomide 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 ▪ pomalidomide in combination with bortezomib and dexamethasone[c, d] ▪ ixazomib in combination with lenalidomide and dexamethasone[d, e] ▪ carfilzomib in combination with dexamethasone taking into account the drugs and drug combinations used in the prior therapies as well as the type and duration of response to the respective prior therapies
2	Adults with relapsed and refractory multiple myeloma who have received at least 4 prior therapies and have demonstrated disease progression on the last therapy; pretreatment includes an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody	Individualized treatment[b] selected from: ▪ carfilzomib in combination with lenalidomide and dexamethasone ▪ elotuzumab in combination with lenalidomide and dexamethasone ▪ elotuzumab in combination with pomalidomide and dexamethasone ▪ daratumumab in combination with bortezomib and dexamethasone ▪ daratumumab in combination with lenalidomide 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 ▪ pomalidomide in combination with bortezomib and dexamethasone[c, d] ▪ ixazomib in combination with lenalidomide and dexamethasone[d, e] ▪ panobinostat in combination with bortezomib and dexamethasone ▪ carfilzomib in combination with dexamethasone ▪ pomalidomide in combination with dexamethasone[f] ▪ lenalidomide in combination with dexamethasone[f] ▪ bortezomib in combination with pegylated liposomal doxorubicin[f] ▪ bortezomib in combination with dexamethasone[f] ▪ daratumumab monotherapy[g] ▪ cyclophosphamide as monotherapy or in combination with dexamethasone[g] ▪ melphalan as monotherapy or in combination with prednisolone or prednisone[g] 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[h, i]

Table 2: Research questions of the benefit assessment of idecabtagene vicleucel (multipage table)

Research question	Therapeutic indication	ACT[a]

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, the duration of response to the prior therapy is a criterion for the individualized therapy. 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.
c. Only for patients who are refractory to a CD38 antibody and lenalidomide.
d. The use of the combination in the context of individualized therapy must be justified based on the type and duration of response to the respective prior therapies in accordance with the specified restrictions.
e. Only for patients who are refractory to bortezomib, carfilzomib and a CD38 antibody.
f. Only for at least double-refractory patients for whom triplet therapy is not suitable.
g. Only for at least triple-refractory patients for whom triplet or doublet therapy is not suitable.
h. 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.
i. 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.

ACT: appropriate comparator therapy; CD: cluster of differentiation; CR: complete response; G-BA: Federal Joint Committee; PR: partial response; VGPR: very good partial response

The G-BA adjusted the ACT according to Table 2 on 26 March 2024, shortly before the company submitted the dossier. In the present dossier, the company therefore deviated from the ACT and followed the originally specified ACT from the consultation meeting with the G-BA of 11 January 2023, in which only one research question was defined for the entire therapeutic indication. For this research question, the ACT at that time consisted of a selection of several equally appropriate drug combinations of a monoclonal antibody, an immunomodulator and a proteasome inhibitor with dexamethasone or pegylated liposomal doxorubicin.

The present assessment is conducted in comparison with the ACT specified by the G-BA on 26 March 2024. The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

No suitable data are available in the company's dossier for either of the 2 research questions specified by the G-BA. However, this is not solely due to the short-term adjustment of the ACT by the G-BA and the associated non-implementation by the company. The following assessment is carried out jointly for both research questions specified by the G-BA.

Results

In agreement with the company, the randomized controlled trial (RCT) KarMMa-3, which included potentially relevant subpopulations for each of the 2 research questions, was identified in the check.

The RCT KarMMa-3 is a potentially relevant study for the benefit assessment of idecabtagene vicleucel. However, no data suitable for the benefit assessment are available in the company's dossier. One reason for this is that the implementation of the ACT for the 2 research questions cannot be assessed based on the information available in the dossier. Another reason is that the data presented on the outcomes of morbidity, health-related quality of life and side effects are not suitable for the benefit assessment. This is justified below.

Evidence provided by the company

The company presented analyses for the total population of the KarMMa-3 study, and on this basis derived an added benefit for the entire therapeutic indication of idecabtagene vicleucel. The KarMMa-3 study is an ongoing, open-label RCT in adult patients with relapsed and refractory multiple myeloma comparing idecabtagene vicleucel versus treatment as per investigator's discretion taking into account their most recent treatment regimen, and selecting from daratumumab in combination with pomalidomide and dexamethasone (DPd), daratumumab in combination with bortezomib and dexamethasone (DVd), ixazomib in combination with lenalidomide and dexamethasone (IRd), carfilzomib in combination with dexamethasone (Kd) or elotuzumab in combination with pomalidomide and dexamethasone (EPd).

The KarMMa-3 study included adult patients with relapsed and refractory multiple myeloma with 2 to 4 prior therapies and an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1. Patients must have received prior treatment with daratumumab, a proteasome inhibitor and an immunomodulatory compound-containing regimen for at least 2 consecutive cycles, and their disease had to be refractory to the last treatment regimen. Only patients considered by the investigator to be candidates for any of the treatment options (DPd, DVd, IRd, Kd or EPd) proposed in the control arm could be included in the study.

Overall, 386 patients were included in the study and randomly allocated in a 2:1 ratio to either treatment with idecabtagene vicleucel (N = 254) or a comparator therapy selected from DPd, DVd, IRd, Kd or EPd (N = 132). A total of 261 (68%) patients had received 2 to 3 prior therapies, and 125 (32%) patients had received 4 prior therapies.

Idecabtagene vicleucel treatment was largely in compliance with the specifications of the Summary of Product Characteristics (SPC). Within 7 days of randomization, patients underwent unstimulated leukapheresis, followed by lymphodepleting chemotherapy. In the time between leukapheresis and lymphodepleting chemotherapy, patients could receive

bridging myeloma therapy for disease control, if needed. The last dose of bridging therapy had to be administered at least 14 days before the initiation of lymphodepleting chemotherapy.

Treatment with the respective drug combinations in the control arm was also carried out largely in compliance with the corresponding SPCs.

From Amendment 2 of the study protocol dated 17 December 2019, upon request by the investigator, patients in the control arm could be switched to treatment with idecabtagene vicleucel after disease progression (determined by an Independent Response Committee [IRC] based on the International Myeloma Working Group [IMWG] criteria) and if eligible, and could receive bridging therapy until the infusion to stabilize their disease.

The primary outcome of the KarMMa-3 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.

Approach of the company

In accordance with the originally specified ACT, the company presented analyses on the total population for all patient-relevant outcomes and used the KarMMa-3 study for the entire therapeutic indication without differentiating between the research questions specified by the G-BA. In the KarMMa-3 study, potentially relevant subpopulations are available for both research question 1 (2 to 3 prior therapies) and research question 2 (≥ 4 prior therapies) of the G-BA. Information on patient characteristics, outcome-specific observation periods or response rates of patient-reported questionnaires for the respective subpopulation is not available.

Relevant information is lacking for both research questions to assess sufficient implementation of the ACT. This can be explained by the short-term modification of the ACT prior to dossier submission. However, this information is necessary to assess the implementation of the applicable ACT. Regardless of this, the analyses presented on the outcomes of morbidity, health-related quality of life and side effects are not suitable for the benefit assessment.

Implementation of the ACT in the KarMMa-3 cannot be assessed

The ACT specified by the G-BA for both research questions was individualized therapy, taking into account the drugs and drug combinations used in the prior therapies as well as the type and duration of response to the respective prior therapies. For research question 2, the general condition must additionally be taken into account, according to the G-BA. Depending on the research question, several triple and dual combinations or monotherapies are possible ACT options. According to the G-BA, any restriction of treatment options in the context of a study of direct comparison must be justified.

Patients with 2 to 3 as well as 4 prior therapies were included in the KarMMa-3 study, but without an analysis by the company according to the 2 research questions of the applicable ACT, it is unclear in which other patient characteristics these patients may differ. However, the patients included in the KarMMa-3 study are a heterogeneous patient population simply due to the different number of prior therapies, which must be taken into account when selecting the comparator therapy. Irrespective of the number of prior therapies and other patient-specific factors, investigators in the KarMMa-3 study had 5 drug combinations at their disposal (DPd, DVd, IRd, Kd and EPd), which are listed among the ACT options as part of a patient-specific therapy for both research questions. According to the inclusion criteria, only patients for whom one of the 5 drug combinations was a suitable treatment option were to be included in the study. However, the information available in the dossier does not show which patient-specific criteria were used to select one of the 5 treatment options. The information provided by the company in the dossier only indicates that refractoriness in the most recent line of therapy was considered as the sole criterion for the choice of comparator therapy and that a different drug combination was to be chosen accordingly. In the present therapeutic indication, the choice of therapy depends on several patient-specific factors, so that without further information it cannot be assessed whether the patients for research questions 1 and 2 received individualized therapy corresponding to the ACT.

Irrespective of the missing information for the subpopulations for research questions 1 and 2, based on the information for the total population, the selected therapy in the comparator arm does not meet the requirements of the ACT and the recommendations of the S3 guideline for some of the patients. It is unclear how these patients are distributed between the 2 research questions. For example, without knowledge of other patient-specific factors, such as duration of response in prior therapies, comorbidities or tolerability, the administration of DPd or DVd is not comprehensible for all patients based on the available information.

Summary

Based on the available information, it cannot be assessed whether the treatment options used in the control arm are an adequate implementation of individualized treatment for all patients in the KarMMa-3 study for research questions 1 and 2, taking into account the drugs and drug combinations used in the prior therapies and the type and duration of response to the respective prior therapies, and additionally the general condition in patients with at least 4 prior therapies. In principle, it would be conceivable to draw conclusions based on the present multicomparator study KarMMa-3 for a subpopulation of the 2 research questions for whom the selection of DPd, DVd, IRd, Kd and EPd is an adequate individualized therapy.

Company's analyses of the outcomes of morbidity, health-related quality of life, and side effects

Irrespective of the lack of analyses for research questions 1 and 2 and the unclear implementation of the ACT in the KarMMa-3 study, no suitable data are available for the outcomes of morbidity, health-related quality of life, and side effects. This is explained below.

Notes on the outcomes of morbidity and health-related quality of life

In the KarMMa-3 study, the patient-reported outcomes on symptoms and health-related quality of life were recorded using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and the EORTC Quality of Life Questionnaire-Multiple Myeloma Module 20 (QLQ-MY20), and health status using the EQ-5D visual analogue scale (VAS).

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

In the KarMMa-3 study, the treatment regimens differed between the study arms. In the control arm, treatment could be initiated immediately after randomization. In the intervention arm, however, idecabtagene vicleucel had to be prepared in advance, and leukapheresis and lymphodepleting chemotherapy had to be carried out. During this period, patients often received optional bridging therapy for disease control. Leukapheresis, bridging therapy and lymphodepleting chemotherapy are to be seen as part of the treatment concept and should therefore be taken into account in the recording of patient-reported outcomes.

In the intervention arm, patient-reported outcomes after randomization were first recorded again within 3 days before lymphodepleting chemotherapy, then on the day of infusion of idecabtagene vicleucel, and then monthly. The time points of recording of patient-reported outcomes did not cover leukapheresis and bridging therapy or the immediate period after idecabtagene vicleucel infusion in the intervention arm. In the control arm however, post-baseline recordings already started at the beginning of the first treatment cycle. Any deterioration in the intervention arm could be observed only notably later than in the control arm due to the delayed recording at the time of lymphocyte depletion. Overall, the results for the patient-reported outcomes are therefore not meaningfully interpretable due to the recording scheme.

Notes on side effect outcomes

Consideration of selectively surveyed AEs that were recorded beyond progression is not appropriate

In the KarMMa-3 study, adverse events (AEs), serious AEs (SAEs) and severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3) were observed in both arms from receipt of informed consent for at least 6 months after infusion with idecabtagene vicleucel or the first dose of the comparator therapy, regardless of progression or treatment

discontinuation. From Month 7 onwards, only SAEs, severe AEs and some specific AEs prespecified by the company were observed up to 28 days after disease progression. Subsequently, SAEs, severe AEs and specific AEs were recorded in both treatment arms until the end of the study only if they were attributed by the investigators to treatment with the study medication. However, patients in the control arm who received idecabtagene vicleucel as subsequent therapy after disease progression were observed for all AEs for an additional 3 months after idecabtagene vicleucel infusion.

The company presented time-to-event analyses in which all events recorded in the study were taken into account. This approach is not appropriate for 2 reasons. Firstly, in the control arm, all events under subsequent therapy with idecabtagene vicleucel were included in the analyses also beyond Month 6, whereas events under other subsequent therapies in the control arm and all subsequent therapies in the intervention arm were only systematically recorded until Month 6 and were included in the analyses. Secondly, the analyses also included AEs that occurred after the first 6 months and subsequent progression plus 28 days, provided that the investigators established a causal relationship with the study medication.

It is not possible to assess the extent to which the 2 aspects described affect the results of the side effects outcomes. The presented analyses are overall not usable for benefit assessment.

Results on added benefit

Since no suitable data are currently available for the benefit assessment on the basis of the available information, there is no hint of an added benefit of idecabtagene vicleucel in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 shows a summary of probability and extent of the added benefit of idecabtagene vicleucel.

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

Table 3: Idecabtagene vicleucel – probability and extent of added benefit (multipage table)

Research question	**Therapeutic indication**	**ACT**[a]	**Probability and extent of added benefit**
1	Adults with relapsed and refractory multiple myeloma who have received 2 to 3 prior therapies and have demonstrated disease progression on the last therapy; pretreatment includes an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody	Individualized treatment[b] selected from: ▪ carfilzomib in combination with lenalidomide and dexamethasone ▪ elotuzumab in combination with lenalidomide and dexamethasone ▪ elotuzumab in combination with pomalidomide and dexamethasone ▪ daratumumab in combination with bortezomib and dexamethasone ▪ daratumumab in combination with lenalidomide 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 ▪ pomalidomide in combination with bortezomib and dexamethasone[c, d] ▪ ixazomib in combination with lenalidomide and dexamethasone[d, e] ▪ carfilzomib in combination with dexamethasone taking into account the drugs and drug combinations used in the prior therapies as well as the type and duration of response to the respective prior therapies	Added benefit not proven

Table 3: Idecabtagene vicleucel – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
2	Adults with relapsed and refractory multiple myeloma who have received at least 4 prior therapies and have demonstrated disease progression on the last therapy; pretreatment includes an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody	Individualized treatment[b] selected from: ▪ carfilzomib in combination with lenalidomide and dexamethasone ▪ elotuzumab in combination with lenalidomide and dexamethasone ▪ elotuzumab in combination with pomalidomide and dexamethasone ▪ daratumumab in combination with bortezomib and dexamethasone ▪ daratumumab in combination with lenalidomide 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 ▪ pomalidomide in combination with bortezomib and dexamethasone[c, d] ▪ ixazomib in combination with lenalidomide and dexamethasone[d, e] ▪ panobinostat in combination with bortezomib and dexamethasone ▪ carfilzomib in combination with dexamethasone ▪ pomalidomide in combination with dexamethasone[f] ▪ lenalidomide in combination with dexamethasone[f] ▪ bortezomib in combination with pegylated liposomal doxorubicin[f] ▪ bortezomib in combination with dexamethasone[f] ▪ daratumumab monotherapy[g] ▪ cyclophosphamide as monotherapy or in combination with dexamethasone[g] ▪ melphalan as monotherapy or in combination with prednisolone or prednisone[g] 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[h, i]	Added benefit not proven

Table 3: Idecabtagene vicleucel – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
a. Presented is the respective ACT specified by the G-BA. b. According to the G-BA, the duration of response to the prior therapy is a criterion for the individualized therapy. 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. c. Only for patients who are refractory to a CD38 antibody and lenalidomide. d. The use of the combination in the context of individualized therapy must be justified based on the type and duration of response to the respective prior therapies in accordance with the specified restrictions. e. Only for patients who are refractory to bortezomib, carfilzomib and a CD38 antibody. f. Only for at least double-refractory patients for whom triplet therapy is not suitable. g. Only for at least triple-refractory patients for whom triplet or doublet therapy is not suitable. h. 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. i. 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. ACT: appropriate comparator therapy; CD: cluster of differentiation; CR: complete response; G-BA: Federal Joint Committee; PR: partial response; VGPR: very good partial response			

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 2022. In that assessment, the G-BA had determined a non-quantifiable added benefit of idecabtagene vicleucel for the research question of adult patients with relapsed and refractory multiple myeloma who have received at least 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy. 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 this report is to assess the added benefit of idecabtagene vicleucel compared with the ACT in adult patients with relapsed and refractory multiple myeloma who have received at least 2 prior therapies, including an immunomodulatory agent, a proteasome inhibitor and a CD38 antibody and have demonstrated disease progression on the last therapy.

The research questions shown in Table 4 result from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of idecabtagene vicleucel (multipage table)

Research question	Therapeutic indication	ACT[a]
1	Adults with relapsed and refractory multiple myeloma who have received 2 to 3 prior therapies and have demonstrated disease progression on the last therapy; pretreatment includes an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody	Individualized treatment[b] selected from: ▪ carfilzomib in combination with lenalidomide and dexamethasone ▪ elotuzumab in combination with lenalidomide and dexamethasone ▪ elotuzumab in combination with pomalidomide and dexamethasone ▪ daratumumab in combination with bortezomib and dexamethasone ▪ daratumumab in combination with lenalidomide 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 ▪ pomalidomide in combination with bortezomib and dexamethasone[c, d] ▪ ixazomib in combination with lenalidomide and dexamethasone[d, e] ▪ carfilzomib in combination with dexamethasone taking into account the drugs and drug combinations used in the prior therapies as well as the type and duration of response to the respective prior therapies
2	Adults with relapsed and refractory multiple myeloma who have received at least 4 prior therapies and have demonstrated disease progression on the last therapy; pretreatment includes an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody	Individualized treatment[b] selected from: ▪ carfilzomib in combination with lenalidomide and dexamethasone ▪ elotuzumab in combination with lenalidomide and dexamethasone ▪ elotuzumab in combination with pomalidomide and dexamethasone ▪ daratumumab in combination with bortezomib and dexamethasone ▪ daratumumab in combination with lenalidomide 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 ▪ pomalidomide in combination with bortezomib and dexamethasone[c, d] ▪ ixazomib in combination with lenalidomide and dexamethasone[d, e] ▪ panobinostat in combination with bortezomib and dexamethasone ▪ carfilzomib in combination with dexamethasone ▪ pomalidomide in combination with dexamethasone[f] ▪ lenalidomide in combination with dexamethasone[f] ▪ bortezomib in combination with pegylated liposomal doxorubicin[f] ▪ bortezomib in combination with dexamethasone[f] ▪ daratumumab monotherapy[g] ▪ cyclophosphamide as monotherapy or in combination with dexamethasone[g] ▪ melphalan as monotherapy or in combination with prednisolone or prednisone[g] 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[h, i]

Table 4: Research questions of the benefit assessment of idecabtagene vicleucel (multipage table)

Research question	Therapeutic indication	ACT[a]

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, the duration of response to the prior therapy is a criterion for the individualized therapy. 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.
c. Only for patients who are refractory to a CD38 antibody and lenalidomide.
d. The use of the combination in the context of individualized therapy must be justified based on the type and duration of response to the respective prior therapies in accordance with the specified restrictions.
e. Only for patients who are refractory to bortezomib, carfilzomib and a CD38 antibody.
f. Only for at least double-refractory patients for whom triplet therapy is not suitable.
g. Only for at least triple-refractory patients for whom triplet or doublet therapy is not suitable.
h. 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.
i. 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.

ACT: appropriate comparator therapy; CD: cluster of differentiation; CR: complete response; G-BA: Federal Joint Committee; PR: partial response; VGPR: very good partial response

The G-BA adjusted the ACT according to Table 4 on 26 March 2024, shortly before the company submitted the dossier. In the present dossier, the company therefore deviated from the ACT and followed the originally specified ACT from the consultation meeting with the G-BA of 11 January 2023, in which only one research question was defined for the entire therapeutic indication. For this research question, the ACT at that time consisted of a selection of several equally appropriate drug combinations of a monoclonal antibody, an immunomodulator and a proteasome inhibitor with dexamethasone or pegylated liposomal doxorubicin.

The present assessment is conducted in comparison with the ACT specified by the G-BA on 26 March 2024. The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

No suitable data are available in the company's dossier for either of the 2 research questions specified by the G-BA. However, this is not solely due to the short-term adjustment of the ACT by the G-BA and the associated non-implementation by the company. The following assessment is carried out jointly for both research questions specified by the G-BA (see Chapter I 3 to I 5).

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 idecabtagene vicleucel (status: 1 February 2024)
- bibliographical literature search on idecabtagene vicleucel (last search on 1 February 2024)
- search in trial registries/trial results databases for studies on idecabtagene vicleucel (last search on 1 February 2024)
- search on the G-BA website for idecabtagene vicleucel (last search on 15 February 2024)

To check the completeness of the study pool:

- search in trial registries for studies on idecabtagene vicleucel (last search on 11 April 2024); for search strategies, see I Appendix A of the full dossier assessment

In agreement with the company, the RCT KarMMa-3 [3-9] was identified in the check. The KarMMa-3 study included patients with relapsed and refractory multiple myeloma with 2 to 4 prior therapies. Accordingly, subpopulations of the KarMMa-3 study are potentially relevant for both questions (see Table 4).

The RCT KarMMa-3 is a potentially relevant study for the benefit assessment of idecabtagene vicleucel. However, no data suitable for the benefit assessment are available in the company's dossier. One reason for this is that the implementation of the ACT for the 2 research questions cannot be assessed based on the information available in the dossier. Another reason is that the data presented on the outcomes of morbidity, health-related quality of life and side effects are not suitable for the benefit assessment. The study and the uncertainties regarding the implementation of the ACT are described below. In addition, it is described why the data in the outcome categories of morbidity, health-related quality of life and side effects presented with the dossier are unsuitable for the benefit assessment.

Evidence provided by the company

The company presented analyses for the total population of the KarMMa-3 study, and on this basis derived an added benefit for the entire therapeutic indication of idecabtagene vicleucel. The KarMMa-3 study is an ongoing, open-label RCT in adult patients with relapsed and refractory multiple myeloma comparing idecabtagene vicleucel versus treatment as per investigator's discretion taking into account their most recent treatment regimen, and selecting from daratumumab in combination with DPd, DVd, IRd, Kd or EPd. The

characteristics of the study are presented as supplementary information in I Appendix B of the full dossier assessment.

The KarMMa-3 study included adult patients with relapsed and refractory multiple myeloma with 2 to 4 prior therapies and an ECOG PS of 0 or 1. Induction therapy with or without subsequent stem cell transplant and with or without maintenance therapy was considered as one prior regimen. Patients must have received prior treatment with daratumumab, a proteasome inhibitor and an immunomodulatory compound-containing regimen for at least 2 consecutive cycles, and their disease had to be refractory to the last treatment regimen (defined as documented progressive disease during or within 60 days after this regimen). Only patients considered by the investigator to be candidates for any of the treatment options (DPd, DVd, IRd, Kd or EPd) proposed in the control arm could be included in the study.

Overall, 386 patients were included in the study and randomly allocated in a 2:1 ratio to either treatment with idecabtagene vicleucel (N = 254) or a comparator therapy selected from DPd, DVd, IRd, Kd or EPd (N = 132). Randomization was stratified according to age (< 65 years versus ≥ 65 years), the number of prior anti-myeloma regimens (2 versus 3 or 4) and high-risk cytogenetic factors (present versus absent or unknown). The cytogenetic risk factors considered were translocations between chromosomes 4 and 14 (t[4;14]) or between chromosomes 14 and 16 (t[14;16]) or deletion in the short arm of chromosome 17 (del17p). In the KarMMa-3 study, 261 (68%) patients had received 2 to 3 prior therapies, and 125 (32%) patients had received 4 prior therapies.

Idecabtagene vicleucel treatment was largely in compliance with the specifications of the SPC [10]. Unstimulated leukapheresis was performed within 7 days of randomization. Lymphodepleting chemotherapy was given over 3 days on Days 5 to 3 before the infusion of idecabtagene vicleucel. In the KarMMa-3 study, patients received 150 to 450 × 10^6 chimeric antigen receptor [CAR]-positive T cells once. The dose range in the KarMMa-3 study was defined based on the total number of CAR-positive T cells, whereas the dose range according to the approval is defined based on the CAR-positive viable T cells and corresponds to a range of 260 to 500 × 10^6 CAR-positive viable T cells [10]. The company did not provide any information on the ratio of CAR-positive T cells to CAR-positive viable T cells. In the time between leukapheresis and lymphodepleting chemotherapy, patients could receive bridging therapy for disease control, if needed. The bridging therapy consisted of one cycle of one of the drug combinations available in the control arm, which the patients would have received if they had been allocated to the control arm and which was determined prior to randomization. The bridging therapy had to be completed at least 14 days before the initiation of lymphodepleting chemotherapy.

Treatment with the respective drug combinations in the control arm was largely in compliance with the respective SPCs [11-18]. The choice of therapy was made at the discretion of the

investigator before randomization, taking into account the last therapy. In the KarMMa-3 study, daratumumab was administered intravenously both in the DVd combination and in the DPd combination; however, for the DPd combination in the present therapeutic indication, European approval has only been granted for subcutaneous administration of daratumumab. In the control arm, 43 of the 132 (33%) patients received DPd as comparator therapy. The intravenous administration of daratumumab in the DPd combination is of no consequence for the present benefit assessment.

There were no restrictions regarding subsequent antineoplastic therapies. From Amendment 2 of the study protocol dated 17 December 2019, upon request by the investigator, patients in the control arm could be switched to treatment with idecabtagene vicleucel after disease progression (IRC based on the IMWG criteria) and if eligible. These patients could also receive bridging therapy to stabilize their disease. Bridging therapies could include corticosteroids, alkylating agents, immunomodulatory agents, proteasome inhibitors, and/or anti-CD38 antibodies as single agents or in combination, based on the investigator's discretion.

The primary outcome of the KarMMa-3 study was PFS. Patient-relevant secondary outcomes were outcomes in the categories of mortality, morbidity, health-related quality of life, and side effects.

Four data cut-offs were conducted, of which the company analysed and used the most recent data cut-off from 28 April 2023 for the dossier. The company presented the results of the second data cut-off from 18 April 2022 as supplementary information.

Approach of the company

In accordance with the originally specified ACT, the company presented analyses on the total population for all patient-relevant outcomes and used the KarMMa-3 study for the entire therapeutic indication without differentiating between the research questions specified by the G-BA. In the KarMMa-3 study, potentially relevant subpopulations are available for both research question 1 (2 to 3 prior therapies) and research question 2 (≥ 4 prior therapies). Information on patient characteristics, outcome-specific observation periods or response rates of patient-reported questionnaires for the respective subpopulation is not available. Relevant information is lacking for both research questions to assess sufficient implementation of the ACT. This can be explained by the short-term modification of the ACT prior to dossier submission. However, this information is necessary to assess the implementation of the applicable ACT. Regardless of this, the analyses presented on the outcomes of morbidity, health-related quality of life and side effects are not suitable for the benefit assessment (see sections below).

Implementation of the ACT for research questions 1 and 2 in the KarMMa-3 cannot be assessed

The ACT specified by the G-BA for both research questions was individualized therapy, taking into account the drugs and drug combinations used in the prior therapies as well as the type and duration of response to the respective prior therapies. For research question 2, the general condition must additionally be taken into account, according to the G-BA (see also Table 4). For research question 1, triple and dual combinations from the drug classes of monoclonal antibodies, immunomodulators and proteasome inhibitors, each combined with dexamethasone, are possible treatment options in the context of individualized therapy. For research question 2, in addition to these treatment options, further dual combinations from these drug classes with dexamethasone and daratumumab as monotherapy and classic chemotherapeutic agents as combination or monotherapy in the context of individualized therapy are listed. 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.

The current S3 guideline *"Diagnosis, treatment and follow-up of patients with monoclonal gammopathy of undetermined significance (MGUS) or multiple myeloma"* [19] divides the treatment of refractory and relapsed multiple myeloma based on previous relapses into first to third relapse (1 to 3 prior therapies) and > 3 relapses (≥ 4 prior therapies). According to the S3 guideline, the choice of relapse therapy depends not only on prior therapies but also on other patient-specific factors such as refractoriness status, general condition, comorbidities, tolerability and duration of response in prior lines of therapy. Therefore, all drug classes are usually used and combined in an individual sequence. Nevertheless, the S3 guideline strongly recommends triple combination therapy with 2 of 3 new substances (monoclonal antibody, immunomodulator, proteasome inhibitor) and a steroid for patients with 1 to 3 prior therapies, taking into account the increased toxicity. In patients with ≥ 4 prior therapies, however, classic chemotherapeutic agents and combinations with these can be used in addition to the newer drugs [19]. In contrast to the treatment recommendations for patients with 1 to 3 prior therapies, there is no clear recommendation for a dual or triple combination in these late lines of therapy.

Patients with 2 to 3 as well as 4 prior therapies were included in the KarMMa-3 study, but without an analysis by the company according to the 2 research questions of the applicable ACT, it is unclear in which other patient characteristics these patients may differ. However, based on the information in the S3 guideline and the specification of the ACT, the patients included in the KarMMa-3 study are a heterogeneous patient population simply due to the

different number of prior therapies, which must be taken into account when selecting the comparator therapy. Irrespective of the number of prior therapies and other patient-specific factors, investigators in the KarMMa-3 study had 5 drug combinations at their disposal: DPd, DVd, IRd, Kd and EPd. These drug combinations are listed among the ACT options as part of a patient-specific therapy for both research questions (see Table 4). According to the inclusion criteria, only patients for whom one of the 5 drug combinations was a suitable treatment option were to be included in the study. However, the information available in the dossier does not show which patient-specific criteria were used to select one of the 5 treatment options. The information provided by the company in the dossier only indicates that refractoriness in the most recent line of therapy was considered as the sole criterion for the choice of comparator therapy and that a different drug combination was to be chosen accordingly. According to the inclusion criteria, only patients considered to be candidates for any of the treatment options proposed in the control arm were included in the KarMMa-3 study. However, as described above, the choice of therapy depends on several patient-specific factors, so that without further information it cannot be assessed whether the patients for research questions 1 and 2 received individualized therapy corresponding to the ACT. It should also be noted that in the KarMMa-3 study, the EPd and Kd options were not available to the investigators until the 2nd Amendment to the study protocol of 17 December 2019. According to the European Public Assessment Report (EPAR) [20], a total of 68 (18%) of the 386 patients were randomized in the KarMMa-3 study up to the 2nd Amendment to the study protocol, who had thus an even more limited choice of treatment options.

Irrespective of the missing information for the subpopulations for research questions 1 and 2, based on the information for the total population, the selected therapy in the comparator arm does not meet the requirements of the ACT and the recommendations of the S3 guideline for some of the patients. It is unclear how these patients are distributed between the 2 research questions. For example, 50 (38%) patients received a daratumumab-containing comparator therapy (DPd [n = 43] or DVd [n = 7]) in the KarMMa-3 study. Of these patients, 81% (DPd) and 57% (DVd) had a disease that was refractory to daratumumab in the most recent therapy administered. Across all prior therapies, daratumumab refractoriness was 95% (DPd) and 100% (DVd). As described above, the choice of therapy of refractory and relapsed myeloma depends on several patient-specific factors such, including refractoriness to prior therapies. Refractoriness under treatment with a drug does not generally exclude the use of this drug in a subsequent therapy, as long as the therapy contains a component that was already used some time ago, that has not yet been used, or against which no refractoriness is known. Daratumumab was administered to these patients in a different combination in the most recent line of therapy. Against the second component in the respective new regimen in the study, the refractoriness from the most recent prior therapy was 9% (pomalidomide) or 14% (bortezomib). Across all prior therapies, 28% of patients who received DPd had disease refractory to pomalidomide and 29% of patients who received DVd had disease refractory to

bortezomib. Thus, without knowledge of other patient-specific factors, such as duration of response in prior therapies, comorbidities or tolerability, the administration of DPd or DVd is not comprehensible for all patients based on the available information. However, it can be assumed that other treatment options of the ACT would have been possible or potentially more suitable for these patients.

Summary

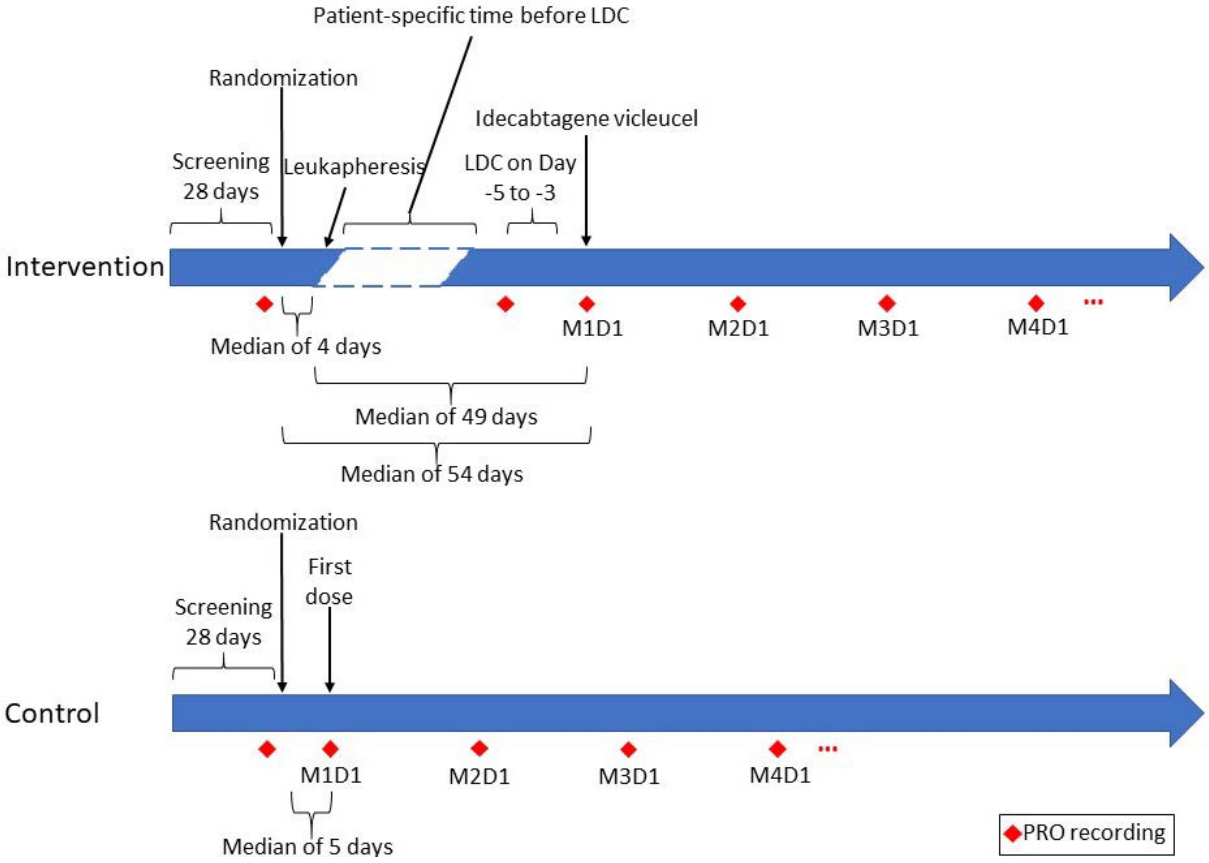
Based on the available information, it cannot be assessed whether the treatment options used in the control arm are an adequate implementation of individualized treatment for all patients in the KarMMa-3 study for research questions 1 and 2, taking into account the drugs and drug combinations used in the prior therapies and the type and duration of response to the respective prior therapies, and additionally the general condition in patients with at least 4 prior therapies. Irrespective of this, it is questionable whether the restriction to the 5 treatment options offered in the KarMMa-3 study enabled individualized treatment corresponding to the ACT for all patients of research questions 1 and 2. In principle, it would be conceivable to draw conclusions based on the present multicomparator study KarMMa-3 for a subpopulation of the 2 research questions for whom the selection of DPd, DVd, IRd, Kd and EPd is an adequate individualized therapy.

Company's analyses of the outcomes of morbidity, health-related quality of life, and side effects

Irrespective of the lack of analyses for research questions 1 and 2 and the unclear implementation of the ACT in the KarMMa-3 study, no suitable data are available for the outcomes of morbidity, health-related quality of life, and side effects. This is explained below.

Notes on the outcomes of morbidity and health-related quality of life

In the KarMMa-3 study, the patient-reported outcomes on symptoms and health-related quality of life were recorded using the EORTC QLQ-C30 and the EORTC QLQ-MY20, and health status using the EQ-5D VAS. The patient-reported outcomes were recorded in both study arms as part of the screening prior to randomization (as baseline). In the intervention arm, a recording was carried out within 3 days before lymphodepleting chemotherapy, on the day of infusion with idecabtagene vicleucel and then monthly on Day 1 until Month 25. In the comparator arm, the recording was carried out on the day the study medication was administered and then monthly on Day 1 (see Figure 1) until Month 25. After Month 25, the recording was carried out in both arms every 3 months (until progression or end of study) or every 6 months for the first 2 years during the survival follow-up. It is a positive aspect that the observation of outcomes on symptoms, health-related quality of life, and health status in the KarMMa-3 study was beyond progression until the end of the study (see Table 8 in I Appendix B of the full dossier assessment).



D: day; LDC: lymphodepleting chemotherapy; M: month; PRO: patient-reported outcome; VAS: visual analogue scale

Figure 1: Schematic presentation of the planned recording time points for patient-reported outcomes in the KarMMa-3 study

In the dossier, the company presented responder analyses for the outcomes on symptoms and health-related quality of life, and on health status. These were operationalized as the time to first deterioration of ≥ 10 or 15 points. It also presented analyses of the mean change in values over the course of the study compared with baseline as supplementary information.

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

In the KarMMa-3 study, the treatment regimens differed between the study arms. While treatment in the control arm could be initiated immediately after randomization, treatment with idecabtagene vicleucel required preparations before administering the individually manufactured CAR T cell product, including leukapheresis, optional bridging therapy, and lymphodepleting chemotherapy. In the period between leukapheresis and CAR T cell infusion, patients in the KarMMa-3 study could receive bridging therapy (84% in the intervention arm received bridging therapy). The median duration from randomization to infusion of idecabtagene vicleucel was 54 days, and 49 days from leukapheresis to idecabtagene vicleucel infusion (see Figure 1). Leukapheresis, bridging therapy and lymphodepleting chemotherapy

are part of the treatment concept, and the associated burden to the patients must therefore be taken into account in the recording of patient-reported outcomes.

In the intervention arm, patient-reported outcomes after randomization were first recorded again within 3 days before lymphodepleting chemotherapy, then on the day of infusion of idecabtagene vicleucel, and then monthly. The time points of recording of patient-reported outcomes did not cover leukapheresis and bridging therapy or the immediate period after idecabtagene vicleucel infusion in the intervention arm. In the control arm however, post-baseline recordings already started at the beginning of the first treatment cycle. The differences in the time points of recording therefore do not allow a fair comparison of the treatment concepts in the treatment arms. This is also shown in the time-to-event analyses presented by the company. Any deterioration in the intervention arm could be observed only notably later than in the control arm due to the delayed beginning of recording at the time of lymphodepleting chemotherapy. Any deterioration, e.g. due to initiation of a bridging therapy in the intervention arm, was therefore not recorded. This can also be seen in the Kaplan-Meier curves presented in Module 4 B, which show a deterioration in the intervention arm only after more than 1 month in all scales of the used instruments (see also Figure 2 in I Appendix C of the full dossier assessment as an example). Overall, the results for the patient-reported outcomes are therefore not meaningfully interpretable due to the recording scheme.

Analyses on patient-reported outcomes planned and presented by the company

In addition to a statistical analysis plan (SAP) for the KarMMa-3 study, the company prepared an SAP for additional analyses of patient-reported outcomes (PRO-SAP). This was finalized on 16 November 2022 and thus after the second data cut-off on 18 April 2022. This PRO-SAP describes, among other things, responder analyses specifically for the early benefit assessment in Germany, which provided for time-to-event analyses for first, confirmed and definitive deterioration, as well as for first, confirmed and definitive improvement. However, the company's dossier only presented time-to-event analyses with the operationalization of time to first deterioration (≥ 10 or 15 points) from the analyses planned according to PRO-SAP. Of these, the company used the time to first deterioration by ≥ 10 points for the instruments EORTC QLQ-C30 and EORTC QLQ-MY20, and the time to first deterioration by ≥ 15 points for the EQ-5D VAS for the benefit assessment. The company did not explain why it only presented the time to first deterioration from the analyses originally planned for the responder analyses. This approach is not appropriate. Since the results of the patient-reported outcomes are not suitable for the benefit assessment in the present data situation (see above), the company's approach is without consequence.

Notes on side effect outcomes

Consideration of selectively surveyed AEs that were recorded beyond progression is not appropriate

In the KarMMa-3 study, AEs, SAEs and severe AEs (CTCAE grade ≥ 3) were observed in both arms from receipt of informed consent for at least 6 months after infusion with idecabtagene vicleucel or the first dose of the comparator therapy, regardless of progression or treatment discontinuation. From Month 7 onwards, only SAEs, severe AEs and some specific AEs prespecified by the company were observed up to 28 days after disease progression. Subsequently, SAEs, severe AEs and specific AEs were recorded in both treatment arms until the end of the study only if they were attributed by the investigators to treatment with the study medication. However, patients in the control arm who received idecabtagene vicleucel as subsequent therapy after disease progression were observed for all AEs for an additional 3 months after idecabtagene vicleucel infusion (see also Table 8 in I Appendix B of the full dossier assessment). At the data cut-off on 28 April 2023, 74 (56%) of the patients in the control arm had received an idecabtagene vicleucel infusion.

In principle, a recording of all AEs over a fixed observation period in both arms, regardless of progression or discontinuation of treatment, as planned by the company, is a positive aspect. Thus, within the 6 months after the first administration of the respective therapy, AEs could be recorded in both arms not only under the respective therapy, but also under any subsequent therapy that the patients received during this period. In principle, however, all AEs should be recorded until the end of the study so that conclusions can be drawn about the entire course of study. In the present situation, however, the planned recording of all AEs within 6 months after the first administration of the respective therapy is notably shortened compared with the median observation period of overall survival in the total population of 31.0 months in the intervention arm and 30.4 months in the control arm.

In Module 4 B of the dossier, the company presented time-to-event analyses in which all events recorded in the study are considered, regardless of whether they were recorded systematically or selectively. This approach is not appropriate for 2 reasons. Firstly, in the control arm, all events under subsequent therapy with idecabtagene vicleucel were included in the analyses also beyond Month 6, whereas events under other subsequent therapies in the control arm and all subsequent therapies in the intervention arm were only systematically recorded until Month 6 after the first administration of treatment in the respective arm and were included in the analyses. Secondly, the analyses also included AEs that occurred after the first 6 months and subsequent progression plus 28 days, provided that the investigators established a causal relationship with the study medication. Due to the need to establish a causal relationship, not all patient-relevant AEs were recorded and included in the analyses, which means that there is no complete picture of all events that occurred. It is not possible to assess the extent to which the 2 aspects described affect the results of the side effects

outcomes. However, it can be inferred from the Kaplan-Meier curves presented in Module 4 B that these aspects may have a relevant influence in particular on the results of the outcome of SAEs (high proportion of events also after Month 6). The presented analyses are overall not usable for benefit assessment.

In the present data situation, analyses of AEs, SAEs and severe AEs over the first 6 months after randomization would be suitable for the benefit assessment because the observation period is comparable between the arms and because all events were systematically recorded. In order to assess the influence AEs selectively recorded after Month 6 following progression (i.e. those under treatment with idecabtagene vicleucel in the control arm or causally related to the study medication in both arms) have on the analyses, analyses with censoring of patients at Month 6 after informed consent or at the time of disease progression plus 28 days, whichever occurs later, should also be presented.

I 4 Results on added benefit

No suitable data are available to assess the added benefit of idecabtagene vicleucel compared with the ACT for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least 2 prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy. There is no hint of added benefit of idecabtagene vicleucel in comparison with the ACT for either research question of the present benefit assessment; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

The result of the assessment of the added benefit of idecabtagene vicleucel in comparison with the ACT is summarized in Table 5.

Table 5: Idecabtagene vicleucel – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adults with relapsed and refractory multiple myeloma who have received 2 to 3 prior therapies and have demonstrated disease progression on the last therapy; pretreatment includes an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody	Individualized treatment[b] selected from: ▪ carfilzomib in combination with lenalidomide and dexamethasone ▪ elotuzumab in combination with lenalidomide and dexamethasone ▪ elotuzumab in combination with pomalidomide and dexamethasone ▪ daratumumab in combination with bortezomib and dexamethasone ▪ daratumumab in combination with lenalidomide 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 ▪ pomalidomide in combination with bortezomib and dexamethasone[c, d] ▪ ixazomib in combination with lenalidomide and dexamethasone[d, e] ▪ carfilzomib in combination with dexamethasone taking into account the drugs and drug combinations used in the prior therapies as well as the type and duration of response to the respective prior therapies	Added benefit not proven

Table 5: Idecabtagene vicleucel – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
2	Adults with relapsed and refractory multiple myeloma who have received at least 4 prior therapies and have demonstrated disease progression on the last therapy; pretreatment includes an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody	Individualized treatment[b] selected from: ▪ carfilzomib in combination with lenalidomide and dexamethasone ▪ elotuzumab in combination with lenalidomide and dexamethasone ▪ elotuzumab in combination with pomalidomide and dexamethasone ▪ daratumumab in combination with bortezomib and dexamethasone ▪ daratumumab in combination with lenalidomide 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 ▪ pomalidomide in combination with bortezomib and dexamethasone[c, d] ▪ ixazomib in combination with lenalidomide and dexamethasone[d, e] ▪ panobinostat in combination with bortezomib and dexamethasone ▪ carfilzomib in combination with dexamethasone ▪ pomalidomide in combination with dexamethasone[f] ▪ lenalidomide in combination with dexamethasone[f] ▪ bortezomib in combination with pegylated liposomal doxorubicin[f] ▪ bortezomib in combination with dexamethasone[f] ▪ daratumumab monotherapy[g] ▪ cyclophosphamide as monotherapy or in combination with dexamethasone[g] ▪ melphalan as monotherapy or in combination with prednisolone or prednisone[g] 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[h, i]	Added benefit not proven

Table 5: Idecabtagene vicleucel – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
a. Presented is the respective ACT specified by the G-BA. b. According to the G-BA, the duration of response to the prior therapy is a criterion for the individualized therapy. 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. c. Only for patients who are refractory to a CD38 antibody and lenalidomide. d. The use of the combination in the context of individualized therapy must be justified based on the type and duration of response to the respective prior therapies in accordance with the specified restrictions. e. Only for patients who are refractory to bortezomib, carfilzomib and a CD38 antibody. f. Only for at least double-refractory patients for whom triplet therapy is not suitable. g. Only for at least triple-refractory patients for whom triplet or doublet therapy is not suitable. h. 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. i. 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. ACT: appropriate comparator therapy; CD: cluster of differentiation; CR: complete response; G-BA: Federal Joint Committee; PR: partial response; VGPR: very good partial response			

The assessment described above departs from that by the company, which derived an indication of considerable added benefit for the entire therapeutic indication of idecabtagene vicleucel, irrespective of the research questions.

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 2022. In that assessment, the G-BA had determined a non-quantifiable added benefit of idecabtagene vicleucel for the research question of adult patients with relapsed and refractory multiple myeloma who have received at least 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy. 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.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 7.0 [online]. 2023 [Accessed: 06.10.2023]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://doi.org/10.1002/bimj.201300274.

3. Bristol-Myers Squibb. A Phase 3, Multicenter, Randomized, Open-Label Study to Compare the Efficacy and Safety of bb2121 Versus Standard Regimens in Subjects with Relapsed and Refractory Multiple Myeloma (RRMM) (KarMMa-3); study BB2121-MM-003; Primary Clinical Study Report [unpublished]. 2023.

4. Bristol-Myers Squibb. A Phase 3, Multicenter, Randomized, Open-Label Study to Compare the Efficacy and Safety of bb2121 Versus Standard Regimens in Subjects with Relapsed and Refractory Multiple Myeloma (RRMM) (KarMMa-3); study BB2121-MM-003; Addendum Overall Survival Report [unpublished]. 2023.

5. Bristol-Myers Squibb. A Phase 3, Multicenter, Randomized, Open-Label Study to Compare the Efficacy and Safety of bb2121 Versus Standard Regimens in Subjects with Relapsed and Refractory Multiple Myeloma (RRMM) (KarMMa-3); study BB2121-MM-003; Overall Survival Report [unpublished]. 2023.

6. Rodriguez-Otero P, Ailawadhi S, Arnulf B et al. Ide-cel or Standard Regimens in Relapsed and Refractory Multiple Myeloma. N Engl J Med 2023; 388(11): 1002-1014. https://doi.org/10.1056/NEJMoa2213614.

7. Delforge M, Patel K, Eliason L et al. Health-related quality of life in patients with triple-class exposed relapsed and refractory multiple myeloma treated with idecabtagene vicleucel or standard regimens; patient-reported outcomes from the phase 3, randomised, open-label KarMMa-3 clinical trial. Lancet Haematol 2024; 11(3): e216-e227. https://doi.org/10.1016/S2352-3026(24)00005-X.

8. Celgene. A Phase 3, Multicenter, Randomized, Open Label Study to Compare the Efficacy and Safety of BB2121 Versus Standard Regimens in Subjects with Relapsed and Refractory Multiple Myeloma (RRMM) (KarMMa-3) [online]. [Accessed: 22.03.2024]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2018-001023-38.

9. Celgene. Efficacy and Safety Study of bb2121 Versus Standard Regimens in Subjects With Relapsed and Refractory Multiple Myeloma (RRMM) (KarMMa-3) [online]. 2022 [Accessed: 22.03.2024]. URL: https://clinicaltrials.gov/study/NCT03651128.

10. Bristol-Myers Squibb. ABECMA 260 – 500 × 10^6 Zellen Infusionsdispersion [online]. 2024 [Accessed: 04.04.2024]. URL: https://www.fachinfo.de.

11. Janssen. VELCADE 3,5 mg Pulver zur Herstellung einer Injektionslösung [online]. 2021 [Accessed: 06.03.2024]. URL: https://www.fachinfo.de/.

12. Bristol-Myers Squibb. REVLIMID Hartkapseln [online]. 2023 [Accessed: 19.04.2024]. URL: https://www.fachinfo.de/.

13. Bristol-Myers Squibb. IMNOVID Hartkapseln [online]. 2023 [Accessed: 06.04.2024]. URL: https://www.fachinfo.de/.

14. Takeda. NINLARO 2,3 mg/3 mg/4 mg Hartkapseln [online]. 2023 [Accessed: 05.04.2023]. URL: https://www.fachinfo.de/.

15. Janssen. DARZALEX 20 mg/ml Konzentrat zur Herstellung einer Infusionslösung [online]. 2023 [Accessed: 05.12.2023]. URL: https://www.fachinfo.de.

16. Janssen. DARZALEX 1800 mg Injektionslösung [online]. 2023 [Accessed: 05.12.2023]. URL: https://www.fachinfo.de.

17. Amgen. Kyprolis 10 mg/30 mg/60 mg Pulver zur Herstellung einer Infusionslösung [online]. 2023 [Accessed: 05.04.2024]. URL: https://www.fachinfo.de/.

18. Bristol-Myers Squibb. Empliciti 300 mg/400 mg Pulver für ein Konzentrat zur Herstellung einer Infusionslösung [online]. 2023 [Accessed: 05.04.2024]. URL: https://www.fachinfo.de/.

19. Leitlinienprogramm Onkologie. Diagnostik, Therapie und Nachsorge für Patienten mit monoklonaler Gammopathie unklarer Signifikanz (MGUS) oder Multiplem Myelom, Langversion 1.0, AWMF-Registernummer: 018/035OL [online]. 2022 [Accessed: 06.12.2023]. URL: https://www.leitlinienprogramm-onkologie.de/leitlinien/multiples-myelom/.

20. European Medicines Agency. Abecma; Assessment report [online]. 2024 [Accessed: 04.04.2024]. URL: https://www.ema.europa.eu/en/documents/variation-report/abecma-h-c-004662-ii-0031-epar-assessment-report-variation_en.pdf.

The full report (German version) is published under https://www.iqwig.de/en/projects/a24-35.html.