Idecabtagene vicleucel (multiple myeloma, ≥ 2 prior therapies)

Addendum to Project A24-35 (dossier assessment)[1]

ADDENDUM

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AESI	adverse event of special interest
CAR	chimeric antigen receptor
CD	cluster of differentiation
cLDA	constrained longitudinal data analysis
CTCAE	Common Terminology Criteria for Adverse Events
DPd	daratumumab in combination with pomalidomide and dexamethasone
DVd	daratumumab in combination with bortezomib and dexamethasone
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
EPd	elotuzumab in combination with pomalidomide and dexamethasone
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HLGT	High Level Group Term
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IRd	ixazomib in combination with lenalidomide and dexamethasone
Kd	carfilzomib in combination with dexamethasone
MedDRA	Medical Dictionary for Regulatory Activities
PRO-SAP	statistical analysis plan for patient-reported outcomes
PT	Preferred Term
R-ISS	Revised International Staging System
RCT	randomized controlled trial
SAE	serious adverse event
SAP	statistical analysis plan
SGB	Sozialgesetzbuch (Social Code Book)
SMQ	Standardized Medical Dictionary for Regulatory Activities [MedDRA] Queries
SOC	System Organ Class
VAS	visual analogue scale

1 Background

On 6 August 2024, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A24-35 (Idecabtagene vicleucel – Benefit assessment according to §35a Social Code Book V) [1].

The commission comprises the assessment of the data subsequently submitted by the pharmaceutical company (hereinafter referred to as the "company") in the commenting procedure [2], taking into account the information in the dossier [3], on:

- subgroup results by number of prior anti-myeloma regimens
- results of the time-to-event analyses for confirmed and definitive deterioration, and for first, confirmed and definitive improvement, which were prespecified in the statistical analysis plan (SAP) for patient-reported outcomes (PRO-SAP), as well as sensitivity analyses investigating the influence of the later start of recording in the idecabtagene vicleucel arm
- results of the additional time-to-event analyses for tolerability and, in addition, the binary analysis for adverse events (AEs) within the first 6 months after randomization and all associated subgroup analyses (2 to 3 versus 4 prior therapies).

Furthermore, the following analyses subsequently submitted by the company after the oral hearing [4] are to be assessed according to the commission:

- further information on the respective time period considered in the intervention and control arm for the sensitivity analysis on the influence of the start of recording in the idecabtagene vicleucel arm, which was subsequently submitted with the written comments, to be able to reassess the relevance of the missing recordings of patient-reported outcomes in the temporal phase of chimeric antigen receptor (CAR) T cell therapy
- further information on patient characteristics with regard to a suitable implementation of individualized therapy
- analyses of specific AEs separately for both research questions in accordance with the dossier template
- subgroup analyses separately for both research questions in accordance with the dossier template

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment of the KarMMa-3 study

The aim of benefit assessment A24-35 [1] was 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. Two research questions result from the ACT specified by the G-BA, separated by number of prior therapies:

- research question 1: patients with 2 to 3 prior therapies
- research question 2: patients with at least 4 prior therapies

In the dossier, the company presented the randomized controlled trial (RCT) KarMMa-3 [5-11] comparing idecabtagene vicleucel with individualized therapy 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). A detailed description of the KarMMa-3 study can be found in dossier assessment A24-35 [1].

As already described in the dossier assessment, the KarMMa-3 study was classified as potentially relevant to the benefit assessment of idecabtagene vicleucel. However, the analyses presented in the company's dossier could not be used for the assessment, partly because analyses were only available for the entire study population and not separately by research question. Furthermore, the implementation of the ACT could not be conclusively assessed on the basis of the information presented in the dossier.

In the following Section 2.1, the information subsequently submitted by the company on the patient characteristics regarding the implementation of the individualized therapy in the comparator arm of the study is first assessed. In addition, the analyses on patient-reported outcomes of morbidity and health-related quality of life as well as on outcomes of side effects subsequently submitted by the company in the comments are assessed with regard to their usability for the benefit assessment. In accordance with research question 1, Section 2.2 presents the results of the relevant subpopulation of the KarMMa-3 study for patients with relapsed and refractory multiple myeloma who have received 2 to 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy. In accordance with research question 2, Section 2.3 presents the results of the relevant subpopulation of the KarMMa-3 study for patients with relapsed and refractory multiple myeloma who have received at least 4 prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-

CD38 antibody and have demonstrated disease progression on the last therapy. The key results for the total population of the KarMMa-3 study are presented as supplementary information in Appendix E.

2.1 Analyses of the KarMMa-3 study subsequently submitted by the company

2.1.1 Implementation of the appropriate comparator therapy in the KarMMa-3 study

In the commenting procedure, the company subsequently submitted information on the patient characteristics of the subpopulations potentially relevant to research question 1 and research question 2 (2 to 3 prior therapies and 4 prior therapies) from the KarMMa-3 study. Based on this information, it can be seen that both subpopulations differed at the beginning of the study, particularly with regard to the time since first diagnosis and refractory status (see Table 1 and Table 12). The mean time since first diagnosis was shorter in the subpopulation relevant to research question 1 than in the subpopulation relevant to research question 2 (approx. 4.4 years versus approx. 5.9 years). The proportions of triple-refractory and penta-refractory patients were lower in the subpopulation relevant to research question 1 than in the subpopulation relevant to research question 2 (56% versus 85% triple-refractory, and 2% versus 13% penta-refractory).

In addition to the information on patient characteristics, the company provided a list of the prior therapies broken down at patient level. It is not possible to assess the implementation of individualized therapy using the treatment options offered in the KarMMa-3 study on the basis of this information alone. According to the G-BA's note on the ACT and to the current S3 guideline *"Diagnosis, treatment and follow-up of patients with monoclonal gammopathy of undetermined significance (MGUS) or multiple myeloma"* [12], prior therapies and refractory status each represent only one aspect in the selection of the optimal treatment for the individual patient. In addition, a variety of disease- and patient-specific factors, including myeloma type, cytogenetics, degree of bone marrow infiltration, general condition, comorbidities, presence of extramedullary disease, tolerability, type and duration of response to prior therapies, etc., must be taken into account in the patient-specific choice of therapy in relapse. The company still did not provide information on this. Depending on these patient-specific factors, a large number of drugs in various combinations are available to patients with relapsed and refractory myeloma according to the S3 guideline, which were not offered in the comparator arm of the KarMMa-3 study except for the 5 treatment options mentioned above. Irrespective of the remaining uncertainties, the 5 treatment options that were available in the KarMMa-3 study are covered by the G-BA's ACT for both research questions and represent relevant treatment options in the present therapeutic indication. Taking into account the written comments [2] and the discussion at the oral hearing [4], it is therefore presumed that the majority of patients included in the KarMMa-3 study received adequate individualized therapy in line with the ACT.

In summary, it remains unclear whether the comparator treatment used in the KarMMa-3 study represents a full implementation of the ACT. The remaining uncertainties did not result in exclusion of the study, however. However, due to these uncertainties in the implementation of the ACT, no more than hints, e.g. of an added benefit, can be derived from the results of the study. Besides, based on the results of the KarMMa-3 study, conclusions on the added benefit of idecabtagene vicleucel can only be drawn for those patients according to research question 1 and research question 2 for whom treatment with DPd, DVd, IPd, Kd or EPd represents the optimal therapy for each individual patient. In addition, conclusions on added benefit for research question 2 are only possible for patients with 4 prior therapies, as no patients with more than 4 prior therapies were included in the KarMMa-3 study.

2.1.2 Analyses of patient-reported outcomes

As justified in the dossier assessment [1], the time-to-event analyses (time to first deterioration) on patient-reported outcomes of symptoms, health status and health-related quality of life presented by the company in Module 4 B of the dossier are not suitable for the benefit assessment. This is mainly due to the notable differences in the time points of recording of these outcomes between the 2 treatment arms and the fact that important treatment phases of leukapheresis and bridging therapy were not recorded in the intervention arm. This difference in recording between the treatment groups is due to the planning and thus to the design of the study, according to which, in the intervention arm, recording of patient-reported outcomes after randomization was not planned again until shortly before lymphodepleting chemotherapy. As a result, events between randomization and lymphodepleting chemotherapy, when the patient-specific CAR T cells were produced and more than 80% of patients received bridging therapy, were not observed.

With the comments, the company submitted all time-to-event analyses planned according to the PRO-SAP (time to first/confirmed/definitive improvement/deterioration). It also presented sensitivity analyses on the time-to-event analyses (time to first deterioration), in which it also took into account the recording before lymphodepleting chemotherapy in the intervention arm.

In the commenting procedure, the company clarified that the analyses in Module 4 B on patient-reported outcomes took into account the first recording after randomization on the day of the infusion of idecabtagene vicleucel in the intervention arm and on the day of the first administration of the comparator therapy in the control arm. In these analyses, the median time from randomization to this recording was 54 days in the intervention arm and 5 days in the control arm. The company now presented analyses which also take into account an earlier recording at the time of lymphodepleting chemotherapy. The median time from randomization to lymphodepleting chemotherapy was 49 days in the intervention arm (see also dossier assessment A24-35 [1]). Thus, the sensitivity analyses shortened the unobserved

period in the intervention arm only to a negligible extent by approx. 5 days compared with the analyses in Module 4 B. The company also submitted an updated graphical representation of the chronological sequence of the recordings of patient-reported outcomes. This diagram also shows that the patient-reported outcomes in the control arm had already been recorded twice after randomization, before recording in the intervention arm took place at the time of lymphodepleting chemotherapy. This means that a change in symptoms, health status or health-related quality of life could be recorded much earlier in patients in the control arm, whereas in the intervention arm, an event could only occur much later due to the delayed time points of recording. Thus, no meaningful comparison between the intervention and control arm is possible. Overall, both the time-to-event analyses presented by the company in Module 4 B of the dossier and those subsequently submitted with the comments (time to first/confirmed/definitive deterioration/improvement) as well as the sensitivity analyses are therefore not suitable for the benefit assessment.

In addition to the time-to-event analyses, the company also submitted results from longitudinal analyses using constrained longitudinal data analysis (cLDA) over the entire course of the study with the comments. It argued that, in contrast to the time-to-event analyses, these would show longer-term and sustained differences between the treatment groups. It also presented cLDA sensitivity analyses up to Month 6 and thus equal observation periods in the treatment groups. Due to the lack of recordings, no values from the period between randomization and lymphodepleting chemotherapy were included in these analyses either. Even if individual time points of recording have less weight overall in the cLDA analysis, these analyses do not allow a meaningful comparison between the intervention and control arm in terms of the research questions, as relevant treatment phases in the intervention arm are not represented.

In summary, the recording of patient-reported outcomes on symptoms, health status and health-related quality of life differed between the treatment arms, and important treatment phases before the lymphodepleting chemotherapy were not recorded in the intervention arm. This is due to the study design and cannot be remedied by the analyses subsequently submitted by the company, so that no usable data are available for these outcomes for both research questions.

2.1.3 Analyses on side effect outcomes

In the study, all events in the outcomes on side effects were systematically recorded in both study arms in the period up to 6 months after randomization. The analyses on outcomes of side effects presented by the company in Module 4 B of the dossier were considered unsuitable for the benefit assessment for 2 main 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 serious AEs (SAEs), severe AEs and specific AEs that were recorded after disease progression after Month 6, provided that the investigators established a causal relationship with the study medication. Thus the time-to-event analyses presented by the company considered all events recorded in the study, regardless of whether they were recorded systematically or selectively. The influence of the selectively recorded events on the analyses could not be assessed (see also dossier assessment A24-35).

With the comments, the company presented time-to-event analyses over the first 6 months after randomization, as well as time-to-event analyses with censoring at Month 6 or disease progression plus 28 days, whichever occurred later, and binary analyses over the period up to 6 months after randomization for the subpopulations relevant to research question 1 and research question 2 as well as for the total population of the KarMMa-3 study for the outcomes of AEs, SAEs and severe AEs. For common AEs by System Organ Class (SOC)/ Preferred Term (PT), separated according to the individual subpopulations, the company presented analyses that corresponded to those in Module 4 B and thus contained potentially selectively recorded events.

In the present data situation, the binary analyses over the period up to 6 months after randomization are used for the outcomes of AEs, SAEs and severe AEs for the benefit assessment. This is mainly due to the fact that the risk of bias for these results is rated as low because of the same observation period between the treatment arms and the complete recording of all AEs, SAEs and severe AEs during this period, regardless of disease progression or discontinuation of treatment. The analyses on AEs, SAEs and severe AEs with censoring at Month 6 or disease progression plus 28 days, whichever occurred later, subsequently submitted by the company are presented as supplementary information (see Appendix C).

The presentation of common AEs according to SOC/PT and the selection of further specific AEs uses the analyses for the individual subpopulations, which contain selectively recorded events, and which were subsequently submitted by the company in the context of the comments. The company presented no further Kaplan-Meier curves for the specific AEs at SOC and PT level for the subpopulations of the 2 research questions except for the AEs of special interest (AESI) prespecified according to the planning of the study. The potential consideration of selectively recorded events in these analyses is taken into account when assessing the risk of bias of the results for specific AEs.

2.2 Research question 1: patients with 2 to 3 prior therapies

2.2.1 Study characteristics

A detailed description of the KarMMa-3 study can be found in dossier assessment A24-35 [1]. The characteristics of the subpopulation of patients with 2 to 3 prior therapies relevant to research question 1 are described below. The results from the most recent data cut-off of 28 April 2023 are considered for the benefit assessment.

Characteristics of the study population

Table 1 shows the characteristics of the patients in the subpopulation of the KarMMa-3 study relevant to research question 1.

Table 1: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 1: patients with 2–3 prior therapies) (multipage table)

Study Characteristic Category	**Idecabtagene vicleucel N = 173**	**Individualized therapy selected from DPd, DVd, IRd, Kd or EPd N = 88**
KarMMa-3		
Age [years]		
Mean (SD)	62 (9)	61 (10)
Age group, n (%)		
< 65 years	104 (60)	52 (59)
≥ 65 years	69 (40)	36 (41)
Sex [F/M], %	38/62	42/58
Family origin, n (%)		
Asian	5 (3)	3 (3)
Black or African American	12 (7)	10 (11)
White	124 (72)	54 (61)
Not reported	29 (17)	18 (21)
Other[a]	3 (2)[b]	3 (3)[b]
ECOG PS, n (%)		
0	84 (49)	45 (51)
1	89 (51)	39 (44)
≥ 2	0 (0)	4 (5)[c]
Time since first diagnosis [years]		
Mean (SD)	4.4 (2.8)	4.3 (2.4)
Median [Q1; Q3]	3.8 [2.7; 5.3]	3.7 [2.8; 5.4]
Revised ISS stage, n (%)		
Stage I	35 (20)	16 (18)
Stage II	100 (58)	56 (64)
Stage III	20 (12)	11 (13)
Unknown or not reported	18 (10)	5 (6)
Cytogenetic risk group, n (%)		
High risk	74 (43)	46 (52)
del(17p)	45 (26)	34 (39)
t(4;14)	32 (19)	14 (16)
t(14;16)	6 (4)	3 (3)
Non-high risk	75 (43)	35 (40)
Unknown or not reported	24 (14)	7 (8)

Table 1: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 1: patients with 2–3 prior therapies) (multipage table)

Study Characteristic Category	**Idecabtagene vicleucel N = 173**	**Individualized therapy selected from DPd, DVd, IRd, Kd or EPd N = 88**
Prior radiation therapy for multiple myeloma, n (%)	62 (36)	23 (26)
Prior surgery for multiple myeloma, n (%)	14 (8)	6 (7)
Prior autologous stem cell transplant, n (%)	147 (85)	76 (86)
1 transplant	120 (69)	66 (75)
> 1 transplant	27 (16)	10 (11)
Number of prior anti-myeloma regimens, n (%)		
2	78 (45)	39 (44)
3	95 (55)	49 (56)
4	0 (0)	0 (0)
Refractory status, n (%)		
IMiD	148 (86)	82 (93)
Lenalidomide	123 (71)	69 (78)
Pomalidomide	75 (43)	40 (46)
Thalidomide	8 (5)	0 (0)
Proteasome inhibitor	113 (65)	59 (67)
Bortezomib	64 (37)	37 (42)
Carfilzomib	53 (31)	23 (26)
Ixazomib/ixazomib citrate	19 (11)	13 (15)
Anti-CD38 antibodies	163 (94)	82 (93)
Daratumumab	163 (94)	82 (93)
Isatuximab	0 (0)	0 (0)
Other	13 (8)	11 (13)
Elotuzumab	9 (5)	8 (9)
Selinexor	2 (1)	3 (3)
Panobinostat	2 (1)	0 (0)
Double-refractory (IMiD and PI), n (%)	97 (56)	55 (63)
Triple-refractory (IMiD, PI, anti-CD38 antibodies), n (%)	93 (54)	54 (61)
Penta-refractory, n (%)	3 (2)	1 (1)
Bone lesions, n (%)		
Yes	131 (76)	67 (76)
No	42 (24)	21 (24)
Unknown or not reported	0 (0)	0 (0)

Table 1: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 1: patients with 2–3 prior therapies) (multipage table)

Study Characteristic Category	**Idecabtagene vicleucel N = 173**	**Individualized therapy selected from DPd, DVd, IRd, Kd or EPd N = 88**
Myeloma type, n (%)		
Any type	146 (84)	79 (90)
IgA	35 (20)	18 (21)
IgD	0 (0)	2 (2)
IgE	0 (0)	0 (0)
IgG	111 (64)	59 (67)
IgM	0 (0)	0 (0)
Not confirmed	27 (16)	9 (10)
Light chain disease, n (%)	24 (14)	7 (8)
Treatment discontinuation, n (%)	0 (0)[c]	79 (90[b])[d]
Study discontinuation, n (%)[e]	71 (41)	20 (23)

a. Includes American or Alaska Natives as well as Native Hawaiians and other Pacific Islanders, among others.
b. Institute's calculation.
c. 14 (8%) of the randomized patients in the intervention arm received leukapheresis but no idecabtagene vicleucel infusion. The most common reason for this was death (10 patients). In addition, 3 (2%) did not receive leukapheresis, so that a total of 17 (10%) of the randomized patients in the intervention arm did not receive an infusion of idecabtagene vicleucel.
d. Common reasons for treatment discontinuation in the control arm were disease progression (82%) and withdrawal of consent (6%). An additional 3 (3%) patients never started treatment.
e. The reasons for study discontinuation in the intervention arm vs. control arm were death (33% vs. 14%) and withdrawal of consent (8% vs. 9%).

CD: cluster of differentiation; DPd: daratumumab in combination with pomalidomide and dexamethasone; DVd: daratumumab in combination with bortezomib und dexamethasone; ECOG PS: Eastern Cooperative Oncology Group Performances Status; EPd: elotuzumab in combination with pomalidomide and dexamethasone; F: female; IgA: immunoglobulin A; IgD: immunoglobulin D; IgE: immunoglobulin E; IgG: immunoglobulin G; IgM: immunoglobulin M; IMiD: immunomodulatory drugs; IRd: ixazomib in combination with lenalidomide and dexamethasone; ISS: International Staging System; Kd: carfilzomib in combination with dexamethasone; M: male; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized patients; PI: proteasome inhibitor; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation

The patient characteristics are largely balanced between the 2 treatment arms. The mean age of the patients was about 62 years, and the majority (68%) were white. In both study arms, the proportion of men (around 61%) was higher than the proportion of women (around 39%). The majority (approx. 80%) of the patients included were classified as Revised International Staging System (R-ISS) stage I or II.

In the intervention arm, 8% of patients did not receive idecabtagene vicleucel infusion despite leukapheresis. The most common reason for this was death (6%). In the control arm, treatment discontinuation occurred in around 90% of patients. The most common reason for this was disease progression (82%). The proportion of patients with study discontinuation was higher in the intervention arm than in the control arm (41% versus 23%). The most common reasons for study discontinuation in both arms were death (33% versus 14%) and withdrawal of consent (8% versus 9%).

Information on the course of the study

Table 2 shows patients' median treatment duration and the median observation period for individual outcomes and outcome categories.

Table 2: Information on the course of the study – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 1: patients with 2–3 prior therapies)

Study **Duration of the study phase** **Outcome category/outcome**	**Idecabtagene vicleucel** **N[a] = 173**	**Individualized therapy selected from DPd, DVd, IRd, Kd or EPd** **N[a] = 88**
KarMMa-3		
Treatment duration	ND	ND
Observation period [months]		
Overall survival[b]		
Median [Q1; Q3]	26.3 [13.7; 32.3]	24.6 [14.2; 30.1]
Mean (SD)	24.6 (12.3)	23.1 (10.9)
Morbidity, health-related quality of life		
EORTC QLQ-C30, EORTC QLQ-MY20, EQ-5D VAS	No suitable data[c]	
Side effects[d]	ND	ND

a. Number of randomized patients.
b. No information is available on how the observation period was calculated.
c. See Section 2.1.2 for an explanation.
d. For the outcomes of SAEs and severe AEs, the analyses of events up to 6 months after randomization subsequently submitted by the company are used for the benefit assessment. For the specific AEs, the subsequently submitted analyses with analogous operationalization to Module 4 B are considered (see also Section 2.1.3).

AE: adverse event; DPd: daratumumab in combination with pomalidomide and dexamethasone; DVd: daratumumab in combination with bortezomib and dexamethasone; EORTC: European Organisation for Research and Treatment of Cancer; EPd: elotuzumab in combination with pomalidomide and dexamethasone; IRd: ixazomib in combination with lenalidomide and dexamethasone; Kd: carfilzomib in combination with dexamethasone; N: number of analysed patients; ND: no data; Q1: first quartile; Q3: third quartile; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation; VAS: visual analogue scale

No data on the duration of treatment are available for the subpopulation of the KarMMa-3 study relevant to research question 1. It should be noted that treatment with idecabtagene vicleucel in the intervention arm consisted of a single infusion. In contrast, all treatment options offered in the control arm were administered until disease progression, unacceptable toxicity or withdrawal of consent. The study documents contain information on the treatment durations of the individual treatment options in the control arm at the earlier data cut-off date of 18 April 2022 for the total population. According to these data, the shortest median treatment duration was 2.8 months for the treatment option of DVd, and the longest median treatment duration was 5.8 months for the treatment options of DPd and Kd (see information on the course of the study in Appendix E).

The median observation period for the outcome of overall survival is comparable between the study arms.

Subsequent therapies

Table 3 shows for research question 1 which subsequent therapies patients received after discontinuing the study medication.

Table 3: Information on subsequent anti-multiple myeloma therapies (≥ 2 patients in ≥ 1 treatment arm) – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 1: patients with 2–3 prior therapies) (multipage table)

Study **Drug class** **Drug**	**Patients with subsequent therapy, n (%)**	
	Idecabtagene vicleucel **N = 173**	**Individualized therapy selected from DPd, DVd, IRd, Kd or EPd** **N = 88**
KarMMa-3 (data cut-off April 2023)		
Total	102 (59.0)	71 (80.7)
Antineoplastic and immunomodulatory drugs	102 (100.0[a])	70 (98.6[a])
Cyclophosphamide	44 (43.1[a])	45 (63.4[a])
Carfilzomib	51 (50.0[a])	37 (52.1[a])
Pomalidomide	45 (44.1[a])	16 (22.5[a])
Idecabtagene vicleucel	0 (0)	51 (71.8[a])
Bortezomib	20 (19.6[a])	18 (25.4[a])
Daratumumab	19 (18.6[a])	15 (21.1[a])
Etoposide	17 (16.7[a])	16 (22.5[a])
Belantamab mafodotin	18 (17.6[a])	9 (12.7[a])
Cisplatin	15 (14.7[a])	12 (16.9[a])
Doxorubicin	9 (8.8[a])	13 (18.3[a])
Elotuzumab	14 (13.7[a])	5 (7.0)
Selinexor	14 (13.7[a])	4 (5.6[a])
Isatuximab	10 (9.8[a])	6 (8.5[a])
Talquetamab	9 (8.8[a])	6 (8.5[a])
Fludarabine	3 (2.9[a])	11 (15.5[a])
Cevostamab	9 (8.8[a])	3 (4.2[a])
Investigational antineoplastic drugs	12 (11.8[a])	0 (0)
Melphalan	6 (5.9[a])	6 (8.5[a])
Elranatamab	7 (6.9[a])	4 (5.6[a])
Lenalidomide	4 (3.9[a])	6 (8.5[a])
Teclistamab	7 (6.9[a])	3 (4.2[a])
Ixazomib	4 (3.9[a])	4 (5.6[a])
Venetoclax	4 (3.9[a])	3 (4.2[a])
Bendamustine	3 (2.9[a])	3 (4.2[a])
Ciltacabtagene autoleucel	3 (2.9[a])	1 (1.4[a])
Daratumumab hyaluronidase fihj	4 (3.9[a])	0 (0)
Vincristine	2 (2.0[a])	2 (2.8[a])
CAR T cells, NOS	1 (1.0[a])	2 (2.8[a])
Carmustine	3 (2.9[a])	0 (0)
Cetrelimab	2 (2.0[a])	1 (1.4[a])

Table 3: Information on subsequent anti-multiple myeloma therapies (≥ 2 patients in ≥ 1 treatment arm) – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 1: patients with 2–3 prior therapies) (multipage table)

Study	**Patients with subsequent therapy, n (%)**	
Drug class **Drug**	**Idecabtagene vicleucel** **N = 173**	**Individualized therapy selected from DPd, DVd, IRd, Kd or EPd** **N = 88**
Iberdomide	3 (2.9[a])	0 (0)
Pembrolizumab	3 (2.9[a])	0 (0)
Thalidomide	0 (0)	3 (4.2[a])
Cytarabine	2 (2.0[a])	0 (0)
Melphalan flufenamide	2 (2.0[a])	0 (0)
Melphalan hydrochloride	2 (2.0[a])	0 (0)
Modakafusp alfa	2 (2.0[a])	0 (0)
Systemic hormonal preparations, excl. sex hormones and insulins	77 (75.5[a])	63 (88.7[a])
Dexamethasone	76 (74.5[a])	63 (88.7[a])
Methylprednisolone	2 (2.0[a])	3 (4.2[a])
Prednisone	3 (2.9[a])	1 (1.4[a])
Further therapies		
Stem cells, NOS	4 (3.9[a])	4 (5.6[a])
Autologous stem cells, NOS	4 (3.9[a])	2 (2.8[a])

a. Institute's calculation based on the proportion of patients with subsequent therapy.

CAR: chimeric antigen receptor; DPd: daratumumab in combination with pomalidomide and dexamethasone; DVd: daratumumab in combination with bortezomib and dexamethasone; EPd: elotuzumab in combination with pomalidomide and dexamethasone; IRd: ixazomib in combination with lenalidomide and dexamethasone; Kd: carfilzomib in combination with dexamethasone; n: number of patients with subsequent therapy; N: number of analysed patients; NOS: not otherwise specified; RCT: randomized controlled trial

At the most recent data cut-off on 28 April 2023, 59.0% of patients in the intervention arm and 80.7% in the control arm had received at least one subsequent anti-multiple myeloma therapy. The therapies administered reflect the variety of treatment options in the therapeutic indication. Notable is the high proportion of patients (71.8%) in the control arm who switched to treatment with idecabtagene vicleucel after disease progression as part of the study. The possibility to receive idecabtagene vicleucel as subsequent therapy is in line with the German health care context because idecabtagene vicleucel had already been approved for 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, before the KarMMa-3 study was conducted, no directly comparative data with the ACT were

available for idecabtagene vicleucel in these late lines of therapy, so that it cannot be conclusively assessed to what extent switching to idecabtagene vicleucel has advantages over other treatment options in the therapeutic indication and was therefore indicated.

Risk of bias across outcomes (study level)

Table 4 shows the risk of bias across outcomes (risk of bias at study level).

Table 4: Risk of bias across outcomes (study level) – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
KarMMa-3	Yes	Yes	No	No	Yes	Yes	Low

DPd: daratumumab in combination with pomalidomide and dexamethasone; DVd: daratumumab in combination with bortezomib and dexamethasone; EPd: elotuzumab in combination with pomalidomide and dexamethasone; IRd: ixazomib in combination with lenalidomide and dexamethasone; Kd: carfilzomib in combination with dexamethasone; RCT: randomized controlled trial

The risk of bias across outcomes is rated as low for the KarMMa-3 study.

Limitations resulting from the open-label study design are described for research question 1 in Section 2.2.2.2 with the outcome-specific risk of bias.

Transferability of the study results to the German health care context

The company stated that the KarMMa-3 study, conducted in Germany and other countries, was primarily carried out in Western industrialized countries (Europe and North America), and that the majority of randomized patients (53.6%) came from United States study centres and 5.2% from German study centres, so that data was available on patients from German study centres as well as from numerous Western industrialized countries with a health care standard comparable to that in Germany. It added that there was no evidence of biodynamic or kinetic differences between the individual population groups and in relation to Germany. Therefore, the company deemed it safe to assume that, even when taking into account the demographic data and characteristics of the patients included, the study results were transferable to the German health care context.

The company did not provide any further information on the transferability of the study results to the German health care context.

2.2.2 Results on added benefit

2.2.2.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - symptoms, recorded using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and EORTC QLQ-Multiple Myeloma Module 20 (MY20)
  - health status, recorded using the EQ-5D visual analogue scale (VAS)
- Health-related quality of life
  - recorded using the EORTC QLQ-C30 and the EORTC QLQ-MY20
- Side effects
  - SAEs
  - severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to AEs
  - cytokine release syndrome
  - severe neurological toxicity
  - infusion-related reactions
  - severe infections
  - secondary malignancies
  - other specific AEs, if any

The choice of patient-relevant outcomes deviates from that made by the company, which used further outcomes in the dossier (Module 4 B).

Table 5 shows the outcomes for which data were available in the included study for research question 1.

Table 5: Matrix of outcomes – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 1: patients with 2–3 prior therapies)

Study	Outcomes												
	Overall survival	Symptoms (EORTC QLQ-C30, EORTC QLQ-MY20)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-MY20)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Cytokine release syndrome	Severe neurological toxicity[b]	Infusion-related reactions	Severe infections[c]	Secondary malignancies[d]	Further specific AEs[a, e]
KarMMa-3	Yes	No[f]	No[f]	No[f]	Yes	Yes	No[g]	No[g]	Yes	No[h]	Yes	Yes	Yes

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. Operationalized as nervous system disorders (SOC, severe AEs [CTCAE grade ≥ 3]).
c. Operationalized as infections and infestations (SOC, severe AEs [CTCAE grade ≥ 3]).
d. Operationalized as haematological malignant tumours (sub-SMQ [narrow]), non-haematological malignant tumours (sub-SMQ [narrow]), haematological tumours of unspecified malignancy (sub-SMQ [narrow]), non-haematological tumours of unspecified malignancy (sub-SMQ [narrow]) and myelodysplastic syndrome (ad hoc PT). The following PTs were excluded: plasma cell leukaemia, plasma cell myeloma in remission, plasma cell leukaemia in remission, plasma cell myeloma, plasma cell myeloma recurrent, plasma cell myeloma refractory, and plasmacytoma.
e. The following events (coded according to MedDRA) are considered in research question 1: respiratory, thoracic and mediastinal disorders (SOC, SAEs), neutropenia (PT, severe AEs), hypophosphataemia (PT, severe AEs), and musculoskeletal and connective tissue disorders (SOC, severe AEs).
f. No suitable data available; see Section 2.1.2 for reasons.
g. No suitable data available; see the following text section for reasons.
h. Outcome not recorded.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; DPd: daratumumab in combination with pomalidomide and dexamethasone; DVd: daratumumab in combination with bortezomib and dexamethasone; EORTC: European Organisation for Research and Treatment of Cancer; EPd: elotuzumab in combination with pomalidomide and dexamethasone; IRd: ixazomib in combination with lenalidomide and dexamethasone; Kd: carfilzomib in combination with dexamethasone; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale

Notes on outcomes

Side effects

SAEs and severe AEs

For the outcomes of SAEs and severe AEs, the analyses of events until Month 6 after randomization subsequently submitted by the company are used. The analyses with events

until Month 6 or disease progression, whichever occurred later, are presented in Appendix C.1 as supplementary information (see also Section 2.1.3).

Discontinuation due to AEs

In Module 4 B of the dossier, the company did not present any analyses on the outcome of discontinuation due to AEs. It justified this by stating that treatment with idecabtagene vicleucel consisted of a single administration, making discontinuation due to AEs after an infusion with idecabtagene vicleucel impossible. In contrast, discontinuation due to AEs because of unacceptable toxicities was possible in the control arm, according to the company. In Module 4 B, the company provided a descriptive presentation of discontinuations due to AEs recorded in the KarMMa-3 study for the total population (see Table 38 in Appendix E.4). The company did not submit separate data for the subpopulations relevant to research question 1 or research question 2. The presentation of discontinuations due to AEs in the total population shows that only few discontinuations due to AEs occurred in both treatment groups. According to the information in the dossier, all treatment discontinuations in the intervention arm were due to bridging therapies. In the present data constellation with only few treatment discontinuations due to AEs, the missing analyses have no consequences for the assessment.

Specific AEs

For the presentation of specific AEs and for the selection of further specific AEs, the analyses subsequently submitted by the company are used separately for the individual subpopulations. The uncertainty that potentially selectively recorded events are included in the analysis after Month 6 is taken into account when assessing the risk of bias (see also Section 2.1.3).

Cytokine release syndrome

According to the study protocol, cytokine release syndrome was operationalized in the KarMMa-3 study using the PT of the same name. However, cytokine release syndrome was only recorded in both study arms for those patients who were treated with idecabtagene vicleucel. Due to this selective recording, no comparison between the study arms is possible. Furthermore, there is no information on whether the symptoms underlying the cytokine release syndrome (e.g. fever) were also systematically recorded as AEs in both treatment arms. It is therefore not ensured that the events underlying the outcome of cytokine release syndrome are represented in the benefit assessment via the specific AEs. This remains without consequence in the present data situation (only few severe or serious events in the PT cytokine release syndrome, see Appendix B).

Infusion-related reactions

According to the study protocol, in the KarMMa-3 study, infusion-related reactions (such as fever, chills, redness) were to be observed separately as potential toxicity that may be caused by treatment with idecabtagene vicleucel and treated according to severity. However, infusion-related reactions were neither systematically recorded in a prespecified operationalization, nor are post hoc analyses conducted by the company available for this specific AE. It is therefore assumed that the events underlying the outcome of infusion-related reactions in the KarMMa-3 study were included in the analyses of AEs (overall rates and specific AEs). The assumption that individual specific AEs are symptoms of an infusion reaction is based on the plausibility of the symptoms and the typically early onset at the time of infusion with idecabtagene vicleucel in the intervention arm or the first infusion, e.g. with daratumumab, in the control arm. Where a statistically significant difference between treatment groups is found for these specific AEs and the frequency thresholds shown in Appendix B are exceeded, the events underlying the outcome of infusion-related reactions are therefore depicted by specific AEs in the benefit assessment.

Severe neurological toxicity

In the KarMMa-3 study, AEs for neurological toxicities were recorded and analysed according to 2 prespecified operationalizations: neurological toxicity (broad) and neurological toxicity (focused). The operationalization of neurological toxicity (broad) included all PTs in the SOCs nervous system disorders and psychiatric disorders. The operationalization of neurological toxicity (focused), on the other hand, included PTs selected by the company, conducting a biological-pharmacological plausibility check and taking into account clinical assessment, for AEs of neurological toxicities that are not more precisely defined. In Module 4 B and in the subsequent submissions to the comments, the company presented analyses for neurological toxicity (CTCAE grade ≥ 3), the operationalization of which is unclear. Irrespective of this, the operationalization of neurological toxicity (broad) is considered too broad and therefore unspecific in the present data situation. The operationalization of neurological toxicity (focused) is not suitable for representing severe neurological disorders due to the lack of specification of the PTs considered and the potentially selective consideration and analysis of events. For the outcome of severe neurological toxicity, the operationalization using nervous system disorders (SOC, severe AEs, [CTCAE grade ≥ 3]) is considered for the assessment.

Severe infections

In the dossier, the company presented analyses on infections that were prespecified as AEs of special interest in the KarMMa-3 study and operationalized as PTs within the SOC of infections and infestations, bacterial infectious disorders (High Level Group Term [HLGT]), fungal infectious disorders (HLGT), viral infectious disorders (HLGT), and infections – pathogen unspecified (HLGT). It remains unclear whether all or only selected PTs from the SOC or the individual HLGTs were taken into account. For the outcome of severe infections, the

operationalization using infections and infestations (SOC, severe AEs [CTCAE grade ≥ 3]) is therefore used for the benefit assessment.

Secondary malignancies

In the KarMMa-3 study, secondary malignancies were recorded using the 2 prespecified operationalizations of secondary primary malignancies and new malignancies, of which the company only presented analyses for the operationalization of new malignancies. Secondary primary malignancies were operationalized as haematological malignant tumours (sub-Standardized Medical Dictionary for Regulatory Activities [MedDRA] Queries [sub-SMQs]) and non-haematological malignant tumours (sub-SMQ), as well as ad hoc PTs with clinical assessment. New malignancies, however, were operationalized as haematological malignant tumours (sub-SMQ [narrow]), non-haematological malignant tumours (sub-SMQ [narrow]), haematological tumours of unspecified malignancy (sub-SMQ [narrow]), non-haematological tumours of unspecified malignancy (sub-SMQ [narrow]) and myelodysplastic syndrome (ad hoc PT). The PTs of plasma cell leukaemia, plasma cell myeloma in remission, plasma cell leukaemia in remission, plasma cell myeloma, plasma cell myeloma recurrent, plasma cell myeloma refractory, and plasmacytoma were excluded. This operationalization is adequate to record secondary malignancies; therefore the analyses presented by the company on the outcome new malignancies are used. It should be noted that the observation period to date in the KarMMa-3 study may not be sufficient to fully represent secondary malignancies.

2.2.2.2 Risk of bias

Table 6 describes the risk of bias for the results of the relevant outcomes for research question 1.

Table 6: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 1: patients with 2–3 prior therapies)

Study		Outcomes												
	Study level	Overall survival	Symptoms (EORTC QLQ-C30, EORTC QLQ-MY20)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-MY20)	SAEs[a]	Severe AEs[a, b]	Discontinuation due to AEs	Cytokine release syndrome	Severe neurological toxicity[c, d]	Infusion-related reactions	Severe infections[c, e]	Secondary malignancies[c, f]	Further specific AEs[b, c, g]
KarMMa-3	L	L	–[h]	–[h]	–[h]	L	L	–[i]	–[i]	H[j]	–[i]	H[j]	H[j]	H[j]

a. Based on analyses of events occurring up to 6 months after randomization.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. Based on analyses of any events occurring within the first 6 months after the infusion of idecabtagene vicleucel or the first dose in the control arm, as well as severe AEs (CTCAE grade ≥ 3), SAEs and AEs of special interest occurring in the period from Month 7 to 28 days after progression. In addition, severe AEs (CTCAE grade ≥ 3), SAEs and AEs of special interest that occurred during follow-up observation and were attributed to the study medication by the investigator, as well as any AEs that occurred in the control arm within 3 months of the treatment switch, were included in the analyses.
d. Operationalized as nervous system disorders (SOC, severe AEs [CTCAE grade ≥ 3]).
e. Operationalized as infections and infestations (SOC, severe AEs [CTCAE grade ≥ 3]).
f. Operationalized as haematological malignant tumours (sub-SMQ [narrow]), non-haematological malignant tumours (sub-SMQ [narrow]), haematological tumours of unspecified malignancy (sub-SMQ [narrow]), non-haematological tumours of unspecified malignancy (sub-SMQ [narrow]) and myelodysplastic syndrome (ad hoc PT). The following PTs were excluded: plasma cell leukaemia, plasma cell myeloma in remission, plasma cell leukaemia in remission, plasma cell myeloma, plasma cell myeloma recurrent, plasma cell myeloma refractory, and plasmacytoma.
g. The following events (coded according to MedDRA) are considered: respiratory, thoracic and mediastinal disorders (SOC, SAEs), neutropenia (PT, severe AEs), hypophosphataemia (PT, severe AEs), and musculoskeletal and connective tissue disorders (SOC, severe AEs).
h. No suitable data available; see Section 2.1.2 for reasons.
i. No suitable data available; see Section 2.2.2.1 for reasons.
j. See Section 2.1.3 for reasons.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; DPd: daratumumab in combination with pomalidomide and dexamethasone; DVd: daratumumab in combination with bortezomib and dexamethasone; EORTC: European Organisation for Research and Treatment of Cancer; EPd: elotuzumab in combination with pomalidomide and dexamethasone; H: high; IRd: ixazomib in combination with lenalidomide and dexamethasone; Kd: carfilzomib in combination with dexamethasone; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale

The outcome-specific risk of bias is rated as low for the results of the outcomes of overall survival, SAEs, and severe AEs.

No suitable data are available for the outcomes of symptoms (recorded via EORTC QLQ-C30 and EORTC QLQ-MY20), health status (recorded via EQ-5D VAS), and health-related quality of life (recorded via EORTC QLQ-C30 and EORTC QLQ-MY20) (see Section 2.1.2 for explanation).

The risk of bias of the results on severe neurological toxicity, severe infections, secondary malignancies and other specific AEs is rated as high due to the selectively recorded events potentially included in the analyses (see Section 2.1.3 for details). No suitable data are available for the outcome of discontinuation due to AEs, cytokine release syndrome and infusion-related reactions (see Section 2.2.2.1).

2.2.2.3 Results

Table 7 and Table 8 summarize the results of the comparison of idecabtagene vicleucel with individualized therapy selecting from DVd, DPd, IPd, Kd or EPd in adult patients with relapsed and refractory multiple myeloma who have received at least 2 to 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

The Kaplan-Meier curves on the time-to-event analyses of the outcomes in the included studies are presented under A.1 in Appendix A. The results on common AEs, SAEs and severe AEs can be found under B.1 in Appendix B. The company did not provide information on discontinuations due to AEs for the subpopulation relevant to research question 1. The results on side effects (censoring at 6 months or at progression, whichever occurred later) are presented under C.1 in Appendix C, and the corresponding Kaplan-Meier curves under D.1 in Appendix D as supplementary information.

Table 7: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 1: patients with 2–3 prior therapies) (multipage table)

Study Outcome category Outcome	Idecabtagene vicleucel		Individualized therapy selected from DPd, DVd, IRd, Kd or EPd		Idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd
	N	Median time to event in months [95% CI][a] Patients with event n (%)	N	Median time to event in months [95% CI][a] Patients with event n (%)	HR [95%-CI]; p-value[b]
KarMMa-3					
Mortality					
Overall survival	173	41.4 [38.7; NC] 67 (39)	88	NA [26.9; NC] 36 (41)	1.07 [0.71; 1.63]; 0.630
Morbidity					
Symptoms (EORTC QLQ-C30, EORTC QLQ-MY20)	No suitable data[c]				
Health status (EQ-5D VAS)	No suitable data[c]				
Health-related quality of life					
EORTC QLQ-C30, EORTC QLQ-MY20	No suitable data[c]				
Side effects[d]					
Cytokine release syndrome	No suitable data[e]				
Severe neurological toxicity[f]	170	NA 16 (9)	85	NA 9 (11)	0.87 [0.38; 1.98]; 0.740[g]
Infusion-related reactions	Outcome not recorded				
Severe infections[h]	170	NA 39 (23)	85	NA 22 (26)	0.94 [0.56; 1.59]; 0.815[g]
Secondary malignancies[i]	170	NA 10 (6)	85	NA 7 (8)	0.70 [0.27; 1.83]; 0.459[j]
Respiratory, thoracic and mediastinal disorders (SOC, SAEs)	170	NA 10 (6)	85	NA [40.1; NC] 12 (14)	0.40 [0.17; 0.93]; 0.028[g]
Neutropenia (PT, severe AEs)	170	1.8 [1.6; 2.0]; 136 (80)	85	5.6 [4.2; 7.6] 65 (76)	1.52 [1.12; 2.06]; 0.007[g]
Hypophosphataemia (PT, severe AEs)	170	NA 34 (20)	85	NA 6 (7)	3.36 [1.41; 8.04]; 0.004[g]

Table 7: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 1: patients with 2–3 prior therapies) (multipage table)

Study Outcome category Outcome	Idecabtagene vicleucel		Individualized therapy selected from DPd, DVd, IRd, Kd or EPd		Idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd
	N	Median time to event in months [95% CI][a] Patients with event n (%)	N	Median time to event in months [95% CI][a] Patients with event n (%)	HR [95%-CI]; p-value[b]
Musculoskeletal and connective tissue disorders (SOC, severe AEs)	170	NA 13 (8)	85	NA 16 (19)	0.38 [0.18; 0.79]; 0.007[g]

a. Kaplan-Meier estimate (OS).
b. HR, CI and p-value: Cox proportional hazards model and log-rank test, stratified by age, number of prior anti-myeloma therapies and high-risk cytogenetic abnormalities.
c. See Section 2.1.2 for reasons.
d. Based on analyses of any events occurring within the first 6 months after the infusion of idecabtagene vicleucel or the first dose in the control arm, as well as severe AEs (CTCAE grade ≥ 3), SAEs and AEs of special interest occurring in the period from Month 7 to 28 days after progression. In addition, severe AEs (CTCAE grade ≥ 3), SAEs and AEs of special interest that occurred during follow-up observation and were attributed to the study medication by the investigator, as well as any AEs that occurred in the control arm within 3 months of the treatment switch, were included in the analyses.
e. No suitable data; see Section 2.2.2.1 for reasons.
f. Operationalized as nervous system disorders (SOC, severe AEs [CTCAE grade ≥ 3]).
g. HR, CI and p-value: Cox proportional hazards model and log-rank test, stratified by age and high-risk cytogenetic abnormalities.
h. Operationalized as infections and infestations (SOC, severe AEs [CTCAE grade ≥ 3]).
i. Operationalized as haematological malignant tumours (sub-SMQ [narrow]), non-haematological malignant tumours (sub-SMQ [narrow]), haematological tumours of unspecified malignancy (sub-SMQ [narrow]), non-haematological tumours of unspecified malignancy (sub-SMQ [narrow]) and myelodysplastic syndrome (ad hoc PT). The following PTs were excluded: plasma cell leukaemia, plasma cell myeloma in remission, plasma cell leukaemia in remission, plasma cell myeloma, plasma cell myeloma recurrent, plasma cell myeloma refractory, and plasmacytoma.
j. Effect, CI: Cox proportional hazards model, p-value: log-rank test; both unstratified.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; DPd: daratumumab in combination with pomalidomide and dexamethasone; DVd: daratumumab in combination with bortezomib and dexamethasone; EORTC: European Organisation for Research and Treatment of Cancer; EPd: elotuzumab in combination with pomalidomide and dexamethasone; HR: hazard ratio; IRd: ixazomib in combination with lenalidomide and dexamethasone; Kd: carfilzomib in combination with dexamethasone; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

Table 8: Results (overall rates of side effects, dichotomous) – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 1: patients with 2–3 prior therapies)

Study Outcome category Outcome	Idecabtagene vicleucel		Individualized therapy selected from DPd, DVd, IRd, Kd or EPd		Idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
KarMMa-3					
Side effects[b]					
AEs (supplementary information)	170	170 (100)	85	84 (99)	–
SAEs	170	76 (45)	85	33 (39)	1.15 [0.84; 1.58]; 0.407
Severe AEs[c]	170	158 (93)	85	71 (84)	1.11 [1.00; 1.23]; 0.020
Discontinuation due to AEs				ND	

a. Institute's calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [13]).
b. Based on analyses of events occurring up to 6 months after randomization.
c. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; DPd: daratumumab in combination with pomalidomide and dexamethasone; DVd: daratumumab in combination with bortezomib and dexamethasone; EPd: elotuzumab in combination with pomalidomide and dexamethasone; IRd: ixazomib in combination with lenalidomide and dexamethasone; Kd: carfilzomib in combination with dexamethasone; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

Due to the uncertainty in the implementation of the ACT (see Section 2.1.1) and due to the high risk of bias in some cases, no more than hints, for example of an added benefit, can be determined for all outcomes on the basis of the available information.

Mortality

Overall survival

No statistically significant difference between treatment groups was shown for the outcome of all-cause mortality. There is no hint of added benefit of idecabtagene vicleucel in comparison with individualized therapy with DVd, DPd, IPd, Kd or EPd; an added benefit is therefore not proven.

Morbidity

Symptoms (recorded using EORTC QLQ-C30 and EORTC QLQ-MY20), health status (recorded using EQ-5D VAS)

No suitable data are available for symptoms (recorded using EORTC QLQ-C30 and EORTC QLQ-MY20) and health status (recorded using EQ-5D VAS), see Section 2.1.2 for reasons). In each case, there is no hint of added benefit of idecabtagene vicleucel in comparison with individualized therapy selecting from DVd, DPd, IPd, Kd or EPd; an added benefit is therefore not proven.

Health-related quality of life (recorded using EORTC QLQ-C30 and EORTC QLQ-MY20)

No suitable data are available for health-related quality of life (recorded using the EORTC QLQ-C30 and EORTC QLQ-MY20) (see Section 2.1.2 for reasons). In each case, there is no hint of added benefit of idecabtagene vicleucel in comparison with individualized therapy selecting from DVd, DPd, IPd, Kd or EPd; an added benefit is therefore not proven.

Side effects

SAEs

No statistically significant difference between treatment groups was found for the outcome of SAEs. There is no hint of greater or lesser harm of idecabtagene vicleucel in comparison with individualized therapy selecting from DVd, DPd, IPd, Kd or EPd; greater or lesser harm is therefore not proven.

Severe AEs

A statistically significant difference to the disadvantage of idecabtagene vicleucel in comparison with individualized therapy selecting from DVd, DPd, IPd, Kd or EPd was shown for the outcome of severe AEs. There is a hint of greater harm of idecabtagene vicleucel in comparison with individualized therapy selecting from DVd, DPd, IPd, Kd or EPd.

Discontinuation due to AEs

No suitable data are available for the outcome of discontinuation due to AEs (see Section 2.2.2.1 for reasons). There is no hint of greater or lesser harm of idecabtagene vicleucel in comparison with individualized therapy selecting from DVd, DPd, IPd, Kd or EPd; greater or lesser harm is therefore not proven.

Specific AEs

Cytokine release syndrome and infusion-related reactions

No suitable data are available for the outcomes of cytokine release syndrome and infusion-related reactions. In each case, there is no hint of greater or lesser harm of idecabtagene

vicleucel in comparison with individualized therapy selecting from DVd, DPd, IPd, Kd or EPd; greater or lesser harm is therefore not proven.

Severe neurological toxicity (CTCAE grade ≥ 3), severe infections (CTCAE grade ≥ 3) and secondary malignancies (AEs)

No statistically significant difference between the treatment groups was shown for the outcomes of severe neurological toxicity (CTCAE grade ≥ 3), severe infections (CTCAE grade ≥ 3), and secondary malignancies (AEs). In each case, there is no hint of greater or lesser harm of idecabtagene vicleucel in comparison with individualized therapy selecting from DVd, DPd, IPd, Kd or EPd; greater or lesser harm is therefore not proven.

Respiratory, thoracic and mediastinal disorders (SAEs)

A statistically significant difference in favour of idecabtagene vicleucel in comparison with individualized therapy selecting from DVd, DPd, IPd, Kd or EPd was shown for the outcome of respiratory, thoracic and mediastinal disorders (SAEs). However, there is an effect modification by the characteristic of sex (see Section 2.2.2.4). For men, there is a hint of added benefit of idecabtagene vicleucel in comparison with individualized therapy selecting from DVd, DPd, IPd, Kd or EPd. For women, there is no hint of added benefit of idecabtagene vicleucel in comparison with individualized therapy selecting from DVd, DPd, IPd, Kd or EPd; an added benefit is therefore not proven.

Musculoskeletal and connective tissue disorders (severe AEs [CTCAE grade ≥ 3])

A statistically significant difference in favour of idecabtagene vicleucel was shown for the outcome of musculoskeletal and connective tissue disorders (severe AEs [CTCAE grade ≥ 3]). There is a hint of lesser harm of idecabtagene vicleucel in comparison with individualized therapy selecting from DVd, DPd, IPd, Kd or EPd.

Neutropenia (severe AEs [CTCAE grade ≥ 3]), hypophosphataemia (severe AEs [CTCAE grade ≥ 3])

A statistically significant difference to the disadvantage of idecabtagene vicleucel in comparison with individualized therapy selecting from DVd, DPd, IPd, Kd or EPd was shown for the outcomes of neutropenia (severe AEs [CTCAE grade ≥ 3]) and hypophosphataemia (severe AEs [CTCAE grade ≥ 3]). For these outcomes, there is a hint of greater harm of idecabtagene vicleucel in comparison with individualized therapy selecting from DVd, DPd, IPd, Kd or EPd.

2.2.2.4 Subgroups and other effect modifiers

The following effect modifiers were considered to be relevant for the present benefit assessment:

- age (< 65 years/≥ 65 years)
- sex (female/male)
- R-ISS (I or II/III)

For the outcomes of overall survival and for the subsequently submitted analyses of the outcomes of SAEs and severe AEs (up to 6 months after randomization), the company did not present any subgroup analyses for the subpopulation relevant to research question 1. This approach is not appropriate but remains of no consequence in the present data situation.

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

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

The results are presented in Table 9. Kaplan-Meier curves on the subgroup results are not available.

Table 9: Subgroups (side effects, time to event) – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 1: patients with 2–3 prior therapies)

Study Outcome Characteristic Subgroup	Idecabtagene vicleucel		Individualized therapy selected from DPd, DVd, IRd, Kd or EPd		Idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd	
	N	Median time to event in months [95% CI][a] Patients with event n (%)	N	Median time to event in months [95% CI][a] Patients with event n (%)	HR [95% CI][b]	p-value[c]
KarMMa-3						
Side effects[d]						
Respiratory, thoracic and mediastinal disorders (SAEs)						
Sex						
Male	107	NA 5 (5)	49	NA [40.1; NC] 11 (22)	0.21 [0.07; 0.60]	0.001
Female	63	NA 5 (8)	36	NA 1 (3)	2.82 [0.33; 24.15]	0.323
Total					Interaction:	0.033[e]

a. Kaplan-Meier estimate.
b. HR and CI: Cox proportional hazards model, unstratified.
c. p-value: log-rank test, unstratified.
d. Based on analyses of any events occurring within the first 6 months after the infusion of idecabtagene vicleucel or the first dose in the control arm, as well as severe AEs (CTCAE grade ≥ 3), SAEs and AEs of special interest occurring in the period from Month 7 to 28 days after progression. In addition, severe AEs (CTCAE grade ≥ 3), SAEs and AEs of special interest that occurred during follow-up observation and were attributed to the study medication by the investigator, as well as any AEs that occurred in the control arm within 3 months of the treatment switch, were included in the analyses.
e. Cox proportional hazards model, unstratified, with treatment, subgroup, and the interaction of treatment x subgroup

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; DPd: daratumumab in combination with pomalidomide and dexamethasone; DVd: daratumumab in combination with bortezomib and dexamethasone; EPd: elotuzumab in combination with pomalidomide and dexamethasone; HR: hazard ratio; IRd: ixazomib in combination with lenalidomide and dexamethasone; Kd: carfilzomib in combination with dexamethasone; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; SAE: serious adverse event

Side effects

Specific AEs

Respiratory, thoracic and mediastinal disorders (SAEs)

For the outcome of respiratory, thoracic and mediastinal disorders (SAEs), there is an effect modification by the characteristic of sex. For men, a statistically significant difference between the treatment arms was shown in favour of idecabtagene vicleucel in comparison with individualized therapy selecting from DVd, DPd, IPd, Kd or EPd. For men, there is a hint of added benefit of idecabtagene vicleucel in comparison with individualized therapy selecting from DVd, DPd, IPd, Kd or EPd. For women, there is no hint of added benefit of idecabtagene vicleucel in comparison with individualized therapy selecting from DVd, DPd, IPd, Kd or EPd; an added benefit is therefore not proven.

2.2.3 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [14].

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

2.2.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.2.2.3 and Section 2.2.2.4 (see Table 10).

Table 10: Extent of added benefit at outcome level: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 1: patients with 2–3 prior therapies) (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	41.4 vs. NA months HR: 1.07 [0.71; 1.63]; p = 0.630	Lesser/added benefit not proven
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30, EORTC QLQ-MY20)	No suitable data[c]	Lesser/added benefit not proven
Health status (EQ-5D VAS)	No suitable data[c]	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30, EORTC QLQ-MY20	No suitable data[c]	Lesser/added benefit not proven
Side effects		
SAEs	45% vs. 39% RR: 1.15 [0.84; 1.58] RR: 0.87 [0.63; 1.19][d]; p = 0.407	Greater/lesser harm not proven
Severe AEs	93% vs. 84% RR: 1.11 [1.00; 1.23] RR: 0.90 [0.81; 1.00][d]; p = 0.020 Probability: “hint”	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Greater harm[e], extent: “minor”[f]
Discontinuation due to AEs	ND	Greater/lesser harm not proven
Cytokine release syndrome	No suitable data[g]	Greater/lesser harm not proven
Severe neurological toxicity	NA vs. NA HR: 0.87 [0.38; 1.98]; p = 0.740	Greater/lesser harm not proven
Infusion-related reactions	Outcome not recorded	Greater/lesser harm not proven
Severe infections	NA vs. NA HR: 0.94 [0.56; 1.59]; p = 0.815	Greater/lesser harm not proven

Table 10: Extent of added benefit at outcome level: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 1: patients with 2–3 prior therapies) (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Secondary malignancies	NA vs. NA HR: 0.70 [0.27; 1.83]; p = 0.459	Greater/lesser harm not proven
Respiratory, thoracic and mediastinal disorders (SAEs)		
Sex		
Male	NA vs. NA HR: 0.21 [0.07; 0.60]; p = 0.001 Probability: “hint”	Outcome category: serious/severe side effects CI_u < 0.75 Lesser harm; extent: “major”
Female	NA vs. NA HR: 2.82 [0.33; 24.15]; p = 0.323	Greater/lesser harm not proven
Neutropenia (severe AEs)	1.8 vs. 5.6 months HR: 1.52 [1.12; 2.06] HR: 0.66 [0.49; 0.89][d]; p = 0.007 Probability: “hint”	Outcome category: serious/severe side effects CI_u < 0.90 Greater harm; extent: “considerable”
Hypophosphataemia (severe AEs)	NA vs. NA HR: 3.36 [1.41; 8.04] HR: 0.30 [0.12; 0.71][d]; p = 0.004 Probability: “hint”	Outcome category: serious/severe side effects CI_u < 0.75 Greater harm, extent: “major”
Musculoskeletal and connective tissue disorders (severe AEs)	NA vs. NA HR: 0.38 [0.18; 0.79]; p = 0.007 Probability: “hint”	Outcome category: serious/severe side effects CI_u < 0.90 Lesser harm; extent: “considerable”

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. No suitable data are available for this outcome; see Section 2.1.2 for reasons.
d. Institute’s calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit.
e. The result of the statistical test is decisive for the derivation of the added benefit.
f. Discrepancy between CI and p-value probably due to rounding; the extent is rated as “minor”.
g. No suitable data are available for this outcome; see Section 2.2.2.1 for reasons.

Table 10: Extent of added benefit at outcome level: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 1: patients with 2–3 prior therapies) (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; DPd: daratumumab in combination with pomalidomide and dexamethasone; DVd: daratumumab in combination with bortezomib and dexamethasone; EORTC: European Organisation for Research and Treatment of Cancer; EPd: elotuzumab in combination with pomalidomide and dexamethasone; HR. hazard ratio; IRd: ixazomib in combination with lenalidomide and dexamethasone; Kd: carfilzomib in combination with dexamethasone; NA: not achieved; ND: no data; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale		

2.2.3.2 Overall conclusion on added benefit

Table 11 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 11: Positive and negative effects from the assessment of idecabtagene vicleucel in comparison with individualized therapy (research question 1: patients with 2–3 prior therapies)

Positive effects	**Negative effects**
Outcomes with observation over the entire study duration	
–	–
Outcomes with shortened observation period	
Serious/severe side effects ▪ Respiratory, thoracic and mediastinal disorders (SAE): ▫ Sex (men): hint of lesser harm – extent: “major” ▪ Musculoskeletal and connective tissue disorders (severe AE): hint of lesser harm – extent: “considerable”	Serious/severe side effects ▪ Severe AEs: hint of greater harm – extent: “minor” ▪ Neutropenia (severe AE): hint of greater harm – extent: “considerable” ▪ Hypophosphataemia (severe AE): hint of greater harm – extent: “major”
No suitable data are available for the outcome categories of morbidity and health-related quality of life as well as for the outcomes of discontinuation due to AEs, cytokine release syndrome and infusion-related reactions.	
AE: adverse event; SAE: serious adverse event	

Overall, both positive and negative effects, each with the certainty of conclusions “hint” and with different extent, were shown in the category of serious/severe side effects for

idecabtagene vicleucel in comparison with individualized therapy selecting from DPd, DVd, IPd, Kd or EPd. There are no suitable data for the outcome categories of morbidity and health-related quality of life.

Overall, the distribution of positive and negative effects is considered to be balanced. In summary, an added benefit of idecabtagene vicleucel in comparison with the ACT is therefore not proven for patients with relapsed and refractory multiple myeloma who have received 2 to 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.

2.3 Research question 2: patients with at least 4 prior therapies

2.3.1 Study characteristics

A detailed description of the KarMMa-3 study can be found in dossier assessment A24-35 [1]. The characteristics of the subpopulation of patients with at least 4 prior therapies relevant to research question 2 are described below. The results from the most recent data cut-off of 28 April 2023 are considered for the benefit assessment.

Characteristics of the study population

Table 12 shows the characteristics of the patients in the subpopulation of the KarMMa-3 study relevant to research question 2.

Table 12: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 2: patients with ≥ 4 prior therapies) (multipage table)

Study Characteristic Category	**Idecabtagene vicleucel N[a] = 81**	**Individualized therapy selected from DPd, DVd, IRd, Kd or EPd N[a] = 44**
KarMMa-3		
Age [years]		
Mean (SD)	61 (8)	62 (10)
Age group, n (%)		
< 65 years	46 (57)	26 (59)
≥ 65 years	35 (43)	18 (41)
Sex [F/M], %	40/60	36/64
Family origin, n (%)		
Asian	2 (2)	2 (5)
Black or African American	6 (7)	8 (18)
White	48 (59)	24 (55)
Not reported	25 (31)	9 (20)
Other	0 (0)	1 (2)
ECOG PS, n (%)		
0	36 (44)	21 (48)
1	44 (54)	23 (52)
≥ 2	1 (1)[b]	0 (0)
Time since first diagnosis [years]		
Mean (SD)	5.4 (2.9)	6.6 (3.8)
Median [Q1; Q3]	4.9 [3.4; 7.1]	6.1 [4.1; 8.3]
Revised ISS stage, n (%)		
Stage I	15 (19)	10 (23)
Stage II	50 (62)	26 (59)
Stage III	11 (14)	3 (7)
Unknown or not reported	5 (6)	5 (11)
Cytogenetic risk group, n (%)		
High risk	33 (41)	15 (34)
del(17p)	21 (26)	8 (18)
t(4;14)	11 (14)	4 (9)
t(14;16)	2 (2)	1 (2)
Non-high risk	39 (48)	20 (45)
Unknown or not reported	9 (11)	9 (20)
Prior radiation therapy for multiple myeloma, n (%)	28 (35)	23 (52)
Prior surgery for multiple myeloma, n (%)	5 (6)	4 (9)

Table 12: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 2: patients with ≥ 4 prior therapies) (multipage table)

Study Characteristic Category	**Idecabtagene vicleucel N[a] = 81**	**Individualized therapy selected from DPd, DVd, IRd, Kd or EPd N[a] = 44**
Prior autologous stem cell transplant, n (%)	67 (83)	38 (86)
1 transplant	47 (58)	21 (48)
> 1 transplant	20 (25)	17 (39)
Number of prior anti-myeloma regimens, n (%)		
2	0 (0)	0 (0)
3	0 (0)	0 (0)
4	81 (100)	44 (100)
Refractory status, n (%)		
IMiD	76 (94)	42 (95)
Lenalidomide	63 (78)	35 (80)
Pomalidomide	52 (64)	30 (68)
Thalidomide	2 (2)	2 (5)
Proteasome inhibitor	76 (94)	36 (82)
Bortezomib	48 (59)	23 (52)
Carfilzomib	51 (63)	20 (45)
Ixazomib/ixazomib citrate	16 (20)	10 (23)
Anti-CD38 antibodies	79 (98)	42 (95)
Daratumumab	79 (98)	41 (93)
Isatuximab	1 (1)	1 (2)
Other	11 (14)	9 (20)
Elotuzumab	9 (11)	8 (18)
Selinexor	1 (1)	0 (0)
Panobinostat	1 (1)	1 (2)
Double-refractory (IMiD and PI), n (%)	72 (89)	36 (82)
Triple-refractory (IMiD, PI, anti-CD38 antibodies), n (%)	71 (88)	35 (80)
Penta-refractory, n (%)	12 (15)	4 (9)
Bone lesions, n (%)		
Yes	63 (78)	37 (84)
No	17 (21)	7 (16)
Unknown or not reported	1 (1)	0 (0)

Table 12: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 2: patients with ≥ 4 prior therapies) (multipage table)

Study Characteristic Category	**Idecabtagene vicleucel N[a] = 81**	**Individualized therapy selected from DPd, DVd, IRd, Kd or EPd N[a] = 44**
Myeloma type, n (%)		
Any type	71 (88)	34 (77)
IgA	15 (19)	4 (9)
IgD	0 (0)	0 (0)
IgE	0 (0)	0 (0)
IgG	55 (68)	30 (68)
IgM	1 (1)	0 (0)
Not confirmed	10 (12)	9 (20)
Missing/unknown	0 (0)	1 (2)
Light chain disease, n (%)	10 (12)	9 (20)
Treatment discontinuation, n (%)	0 (0)[c]	40 (91[b])[d]
Study discontinuation, n (%)[e]	47 (58)	18 (41)

a. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Institute's calculation.
c. 10 (12%) of the randomized patients in the intervention arm received leukapheresis but no idecabtagene vicleucel infusion. The most common reason for this was death (9 patients). In addition, 2 (2%) patients did not receive leukapheresis, so that a total of 12 (15%) patients in the intervention arm did not receive an infusion of idecabtagene vicleucel.
d. Common reasons for treatment discontinuation in the control arm were disease progression (77%) and death (7%). An additional 3 (7%) patients never started treatment.
e. Common reasons for study discontinuation in the intervention arm vs. control arm were death (46% vs. 30%) and withdrawal of consent (11% vs. 11%).

CD: cluster of differentiation; DPd: daratumumab in combination with pomalidomide and dexamethasone; DVd: daratumumab in combination with bortezomib und dexamethasone; ECOG PS: Eastern Cooperative Oncology Group Performances Status; EPd: elotuzumab in combination with pomalidomide and dexamethasone; F: female; IgA: immunoglobulin A; IgD: immunoglobulin D; IgE: immunoglobulin E; IgG: immunoglobulin G; IgM: immunoglobulin M; IMiD: immunomodulatory drugs; IRd: ixazomib in combination with lenalidomide and dexamethasone; ISS: International Staging System; Kd: carfilzomib in combination with dexamethasone; M: male; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized patients; PI: proteasome inhibitor; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation

The patient characteristics are largely balanced between the 2 treatment arms. The mean age of the patients was about 61 years, and the majority (58%) were white. In both study arms, the proportion of men (around 62%) was higher than the proportion of women (around 38%).

The majority (approx. 80%) of the included patients were classified as R-ISS stage I or II, and all had undergone 4 prior myeloma therapies.

In the intervention arm, 12% of the randomized patients did not receive idecabtagene vicleucel infusion despite leukapheresis. The most common reason for this was death (11%). In the control arm, treatment discontinuation occurred in around 91% of patients. The most common reasons were disease progression or withdrawal of consent (77% and 7% respectively). The proportion of patients with study discontinuation was higher in the intervention arm than in the control arm (58% versus 41%). The most common reasons for study discontinuation in both arms were death (46% versus 30%) and withdrawal of consent (11% each).

Information on the course of the study

Table 13 shows patients' median treatment duration and the median observation period for individual outcomes and outcome categories.

Table 13: Information on the course of the study – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 2: patients with ≥ 4 prior therapies)

Study **Duration of the study phase** **Outcome category/outcome**	**Idecabtagene vicleucel** **N[a] = 81**	**Individualized therapy selected from DPd, DVd, IRd, Kd or EPd** **N[a] = 44**
KarMMa-3		
Treatment duration	ND	ND
Observation period [months]		
Overall survival[b]		
Median [Q1; Q3]	21.0 [10.2; 28.4]	18.4 [11.0; 27.5]
Mean (SD)	19.6 (11.4)	20.0 (12.2)
Morbidity, health-related quality of life		
EORTC QLQ-C30, EORTC QLQ-MY20, EQ-5D VAS	No suitable data[c]	
Side effects[d]	ND	ND

a. Number of randomized patients.
b. No information is available on how the observation period was calculated.
c. See Section 2.1.2 for an explanation.
d. For the outcomes of SAEs and severe AEs, the analyses of events up to 6 months after randomization subsequently submitted by the company are considered for the benefit assessment. For the specific AEs, the subsequently submitted analyses in accordance with Module 4 B are considered (see also Section 2.1.3).

AE: adverse event; DPd: daratumumab in combination with pomalidomide and dexamethasone; DVd: daratumumab in combination with bortezomib and dexamethasone; EORTC: European Organisation for Research and Treatment of Cancer; EPd: elotuzumab in combination with pomalidomide and dexamethasone; IRd: ixazomib in combination with lenalidomide and dexamethasone; Kd: carfilzomib in combination with dexamethasone; N: number of analysed patients; ND: no data; Q1: first quartile; Q3: third quartile; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation; VAS: visual analogue scale

No data on the duration of treatment are available for the subpopulation of the KarMMa-3 study relevant to research question 2. It should be noted that treatment with idecabtagene vicleucel in the intervention arm consisted of a single infusion. In contrast, all treatment options offered in the control arm were administered until disease progression, unacceptable toxicity or withdrawal of consent. The study documents contain information on the treatment durations of the individual treatment options in the control arm at the earlier data cut-off date of 18 April 2022 for the total population. According to these data, the shortest median treatment duration was 2.8 months for the treatment option of DVd, and the longest median treatment duration was 5.8 months for the treatment options of DPd and Kd (see information on the course of the study in Appendix E).

The median observation period for the outcome of overall survival is comparable between the study arms.

Subsequent therapies

Table 14 shows for research question 2 which subsequent therapies patients received after discontinuing the study medication.

Table 14: Information on subsequent anti-multiple myeloma therapies – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 2: patients with ≥ 4 prior therapies) (multipage table)

Study **Drug class** **Drug**	**Patients with subsequent therapy, n (%)**	
	Idecabtagene vicleucel **N = 81**	**Individualized therapy selected from DPd, DVd, IRd, Kd or EPd** **N = 44**
KarMMa-3 (data cut-off April 2023)		
Total	44 (54.3)	33 (75.0)
Antineoplastic and immunomodulatory drugs	44 (100[a])	33 (100[a])
Cyclophosphamide	13 (29.5[a])	15 (45.5[a])
Carfilzomib	9 (20.5[a])	16 (48.5[a])
Pomalidomide	13 (29.5[a])	7 (21.2[a])
Idecabtagene vicleucel	0 (0)	19 (57.6[a])
Bortezomib	13 (29.5[a])	5 (15.2[a])
Selinexor	10 (22.7[a])	5 (15.2[a])
Etoposide	5 (11.4[a])	8 (24.2[a])
Belantamab mafodotin	7 (15.9[a])	5 (15.2[a])
Cisplatin	4 (9.1[a])	6 (18.2[a])
Doxorubicin	5 (11.4[a])	5 (15.2[a])
Daratumumab	7 (15.9[a])	2 (6.1[a])
Teclistamab	8 (18.2[a])	1 (3.0[a])
Elranatamab	6 (13.6[a])	1 (3.0[a])
Investigational antineoplastic drugs	5 (11.4[a])	2 (6.1[a])
Lenalidomide	2 (4.5[a])	3 (9.1[a])
Bendamustine	0 (0)	4 (12.1[a])
Elotuzumab	3 (6.8[a])	1 (3.0[a])
Fludarabine	1 (2.3[a])	2 (6.1[a])
Isatuximab	2 (4.5[a])	1 (3.0[a])
Melphalan	2 (4.5[a])	1 (3.0[a])

Table 14: Information on subsequent anti-multiple myeloma therapies – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 2: patients with ≥ 4 prior therapies) (multipage table)

Study	**Patients with subsequent therapy, n (%)**	
Drug class		
Drug		
Thalidomide	2 (4.5[a])	1 (3.0[a])
Cevostamab	2 (4.5[a])	0 (0)
Cytarabine	1 (2.3[a])	1 (3.0[a])
Isatuximab-irfc	1 (2.3[a])	1 (3.0[a])
Ixazomib	0 (0)	2 (6.1[a])
Other antineoplastic agents	2 (4.5[a])	0 (0)
Busulfan	1 (2.3[a])	0 (0)
Carmustine	0 (0)	1 (3.0[a])
Ciclosporin	1 (2.3[a])	0 (0)
Dabrafenib	1 (2.3[a])	0 (0)
Eftozanermin alfa	1 (2.3[a])	0 (0)
Fludarabine phosphate	1 (2.3[a])	0 (0)
FOR46	1 (2.3[a])	0 (0)
Iberdomide	1 (2.3[a])	0 (0)
Melphalan flufenamide	1 (2.3[a])	0 (0)
Methotrexate	1 (2.3[a])	0 (0)
Mycophenolate mofetil	1 (2.3[a])	0 (0)
Nivolumab	1 (2.3[a])	0 (0)
Olaparib	1 (2.3[a])	0 (0)
Talquetamab	1 (2.3[a])	0 (0)
Thiotepa	1 (2.3[a])	0 (0)
Tiragolumab	1 (2.3[a])	0 (0)
Trametinib	1 (2.3[a])	0 (0)
Venetoclax	1 (2.3[a])	0 (0)
Systemic hormonal preparations, excl. sex hormones and insulins	37 (84.1[a])	29 (87.9[a])
Dexamethasone	35 (79.5[a])	28 (84.8[a])
Methylprednisolone	1 (2.3[a])	2 (6.1[a])
Prednisone	2 (4.5[a])	1 (3.0[a])
Further therapies		
Stem cells, NOS	3 (6.8[a])	0 (0)
Denosumab	1 (2.3[a])	0 (0)
Autologous stem cells, NOS	0 (0)	1 (3.0[a])

Table 14: Information on subsequent anti-multiple myeloma therapies – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 2: patients with ≥ 4 prior therapies) (multipage table)

Study	**Patients with subsequent therapy, n (%)**
Drug class	
Drug	
a. Institute's calculation based on the proportion of patients with subsequent therapy.	
DPd: daratumumab in combination with pomalidomide and dexamethasone; DVd: daratumumab in combination with bortezomib and dexamethasone; EPd: elotuzumab in combination with pomalidomide and dexamethasone; IRd: ixazomib in combination with lenalidomide and dexamethasone; Kd: carfilzomib in combination with dexamethasone; n: number of patients with subsequent therapy; N: number of analysed patients; NOS: not otherwise specified; RCT: randomized controlled trial	

At the most recent data cut-off on 28 April 2023, 54.3% of patients in the intervention arm and 75.0% in the control arm had received at least one subsequent anti-multiple myeloma therapy. The therapies administered reflect the variety of treatment options in the therapeutic indication. Notable is the high proportion of patients (57.6%) in the control arm who were treated with idecabtagene vicleucel as subsequent therapy. The possibility to receive idecabtagene vicleucel as subsequent therapy is in line with the German health care context because idecabtagene vicleucel had already been approved for 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, before the KarMMa-3 study was conducted, no directly comparative data with the ACT were available for the efficacy of idecabtagene vicleucel in these late lines of therapy, so that it cannot be conclusively assessed to what extent switching to idecabtagene vicleucel has advantages over other treatment options in the therapeutic indication and was therefore indicated.

Risk of bias across outcomes (study level)

The risk of bias across outcomes is rated as low for the KarMMa-3 study (see Table 4).

Limitations resulting from the open-label study design are described for research question 2 in Section 2.3.2.2 with the outcome-specific risk of bias.

Transferability of the study results to the German health care context

The company's information on the transferability of the study results to the German health care context can be found in Section 2.2.1.

2.3.2 Results on added benefit

2.3.2.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - symptoms, recorded using the EORTC QLQ-C30 and EORTC QLQ-MY20
  - health status, recorded using the EQ-5D VAS
- Health-related quality of life
  - recorded using the EORTC QLQ-C30 and the EORTC QLQ-MY20
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - cytokine release syndrome
  - severe neurological toxicity
  - infusion-related reactions
  - severe infections
  - secondary malignancies
  - other specific AEs, if any

The choice of patient-relevant outcomes deviates from that made by the company, which used further outcomes in the dossier (Module 4 B).

Table 15 shows the outcomes for which data were available in the included study for research question 2.

Table 15: Matrix of outcomes – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 2: patients with ≥ 4 prior therapies)

Study	Outcomes												
	Overall survival	Symptoms (EORTC QLQ-C30, EORTC QLQ-MY20)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-MY20)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Cytokine release syndrome	Severe neurological toxicity[b]	Infusion-related reactions	Severe infections[c]	Secondary malignancies[d]	Further specific AEs[a]
KarMMa-3	Yes	No[e]	No[e]	No[e]	Yes	Yes	No[f]	No[f]	Yes	No[g]	Yes	Yes	No[h]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. Operationalized as nervous system disorders (SOC, severe AEs [CTCAE grade ≥ 3]).
c. Operationalized as infections and infestations (SOC, severe AEs [CTCAE grade ≥ 3]).
d. Operationalized as haematological malignant tumours (sub-SMQ [narrow]), non-haematological malignant tumours (sub-SMQ [narrow]), haematological tumours of unspecified malignancy (sub-SMQ [narrow]), non-haematological tumours of unspecified malignancy (sub-SMQ [narrow]) and myelodysplastic syndrome (ad hoc PT). The following PTs were excluded: plasma cell leukaemia, plasma cell myeloma in remission, plasma cell leukaemia in remission, plasma cell myeloma, plasma cell myeloma recurrent, plasma cell myeloma refractory, and plasmacytoma.
e. No suitable data available; see Section 2.1.2 for reasons.
f. No suitable data available; see the following text section for reasons.
g. Outcome not recorded.
h. For research question 2, no further specific AEs were identified based on the AEs occurring in the relevant study.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; DPd: daratumumab in combination with pomalidomide and dexamethasone; DVd: daratumumab in combination with bortezomib and dexamethasone; EORTC: European Organisation for Research and Treatment of Cancer; EPd: elotuzumab in combination with pomalidomide and dexamethasone; IRd: ixazomib in combination with lenalidomide and dexamethasone; Kd: carfilzomib in combination with dexamethasone; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale

The notes on outcomes are identical to those in research question 1 (see Section 2.2.2.1).

2.3.2.2 Risk of bias

Table 16 describes the risk of bias for the results of the relevant outcomes for research question 2.

Table 16: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 2: patients with ≥ 4 prior therapies)

Study		Outcomes												
	Study level	Overall survival	Symptoms (EORTC QLQ-C30, EORTC QLQ-MY20)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-	SAEs[a]	Severe AEs[a, b]	Discontinuation due to AEs	Cytokine release syndrome	Severe neurological toxicity[c, d]	Infusion-related reactions	Severe infections[c, e]	Secondary malignancies[c, f]	Other specific AEs
KarMMa-3	L	L	–[g]	–[g]	–[g]	L	L	–[h]	–[h]	H[i]	–[h]	H[i]	H[i]	–

a. Based on analyses of events occurring up to 6 months after randomization.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. Based on analyses of any events occurring within the first 6 months after the infusion of idecabtagene vicleucel or the first dose in the control arm, as well as severe AEs (CTCAE grade ≥ 3), SAEs and AEs of special interest occurring in the period from Month 7 to 28 days after progression. In addition, severe AEs (CTCAE grade ≥ 3), SAEs and AEs of special interest that occurred during follow-up observation and were attributed to the study medication by the investigator, as well as any AEs that occurred in the control arm within 3 months of the treatment switch, were included in the analyses.
d. Operationalized as nervous system disorders (SOC, severe AEs [CTCAE grade ≥ 3]).
e. Operationalized as infections and infestations (SOC, severe AEs [CTCAE grade ≥ 3]).
f. Operationalized as haematological malignant tumours (SMQ [narrow]), non-haematological malignant tumours (SMQ [narrow]), haematological tumours of unspecified malignancy (SMQ [narrow]), non-haematological tumours of unspecified malignancy (SMQ [narrow]) and myelodysplastic syndrome (ad hoc PT). The following PTs were excluded: plasma cell leukaemia, plasma cell myeloma in remission, plasma cell leukaemia in remission, plasma cell myeloma, plasma cell myeloma recurrent, plasma cell myeloma refractory, and plasmacytoma.
g. No suitable data available; see Section 2.1.2 for reasons.
h. No suitable data available; see Section 2.2.2.1 for reasons.
i. See Section 2.1.3 for reasons.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; DPd: daratumumab in combination with pomalidomide and dexamethasone; DVd: daratumumab in combination with bortezomib and dexamethasone; EORTC: European Organisation for Research and Treatment of Cancer; EPd: elotuzumab in combination with pomalidomide and dexamethasone; H: high; IRd: ixazomib in combination with lenalidomide and dexamethasone; Kd: carfilzomib in combination with dexamethasone; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale

The outcome-specific risk of bias is rated as low for the results of the outcomes of overall survival, SAEs, and severe AEs.

No suitable data are available for the outcomes of symptoms (recorded via EORTC QLQ-C30 and EORTC QLQ-MY20), health status (recorded via EQ-5D VAS), and health-related quality of life (recorded via EORTC QLQ-C30 and EORTC QLQ-MY20) (see Section 2.1.2 for explanation).

The risk of bias of the results on severe neurological toxicity, severe infections, secondary malignancies and other specific AEs is rated as high due to the selectively recorded events potentially included in the analyses (see Section 2.1.3 for reasons). No suitable data are available for the outcome of discontinuation due to AEs (see Section 2.2.2.1).

2.3.2.3 Results

Table 17 and Table 18 summarize the results of the comparison of idecabtagene vicleucel with individualized therapy selecting from DVd, DPd, IPd, Kd or EPd in adult patients with relapsed and refractory multiple myeloma who have received 4 prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

The Kaplan-Meier curves on the time-to-event analyses of the outcomes in the included study are presented under A.2 in Appendix A. The results on common AEs, SAEs and severe AEs can be found under B.2 in Appendix B. The company did not provide information on discontinuations due to AEs for the subpopulation relevant to research question 2. The results on side effects (censoring at 6 months or at progression, whichever occurred later) are presented under C.2 in Appendix C, and the corresponding Kaplan-Meier curves under D.2 in Appendix D as supplementary information.

Table 17: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 2: patients with ≥ 4 prior therapies) (multipage table)

Study **Outcome category** **Outcome**	**Idecabtagene vicleucel**		**Individualized therapy selected from DPd, DVd, IRd, Kd or EPd**		**Idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd**
	N	**Median time to event in months [95% CI][a]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI][a]** **Patients with event n (%)**	**HR [95%-CI]; p-value[b]**
KarMMa-3					
Mortality					
Overall survival	81	31.0 [14.9; NC] 39 (48)	44	23.4 [15.6; NC] 22 (50)	0.96 [0.57; 1.62]; 0.436
Morbidity					
Symptoms (EORTC QLQ-C30, EORTC QLQ-MY20)	No suitable data[c]				
Health status (EQ-5D VAS)	No suitable data[c]				
Health-related quality of life					
EORTC QLQ-C30, EORTC QLQ-MY20	No suitable data[c]				
Side effects[d]					
Cytokine release syndrome	No suitable data[e]				
Severe neurological toxicity[f]	79	NA 5 (6)	41	NA 6 (15)	0.39 [0.12; 1.28]; 0.106[g]
Infusion-related reactions	Outcome not recorded				
Severe infections[h]	79	NA [20.0; NC] 27 (34)	41	NA [19.4; NC] 14 (34)	0.98 [0.51; 1.88]; 0.951[g]
Secondary malignancies[i]	79	NA 8 (10)	41	NA 3 (7)	1.40 [0.37; 5.27]; 0.621[j]

Table 17: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 2: patients with ≥ 4 prior therapies) (multipage table)

Study Outcome category Outcome	Idecabtagene vicleucel		Individualized therapy selected from DPd, DVd, IRd, Kd or EPd		Idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd
	N	Median time to event in months [95% CI][a] Patients with event n (%)	N	Median time to event in months [95% CI][a] Patients with event n (%)	HR [95%-CI]; p-value[b]

a. Kaplan-Meier estimate (OS).
b. HR, CI and p-value: Cox proportional hazards model and log-rank test, stratified by age, number of prior anti-myeloma therapies and high-risk cytogenetic abnormalities.
c. See Section 2.1.2 for reasons.
d. Based on analyses of any events occurring within the first 6 months after the infusion of idecabtagene vicleucel or the first dose in the control arm, as well as severe AEs (CTCAE grade ≥ 3), SAEs and AEs of special interest occurring in the period from Month 7 to 28 days after progression. In addition, severe AEs (CTCAE grade ≥ 3), SAEs and AEs of special interest that occurred during follow-up observation and were attributed to the study medication by the investigator, as well as any AEs that occurred in the control arm within 3 months of the treatment switch, were included in the analyses.
e. No suitable data; see Section 2.2.2.1 for reasons.
f. Operationalized as nervous system disorders (SOC, severe AEs [CTCAE grade ≥ 3]).
g. HR, CI and p-value: Cox proportional hazards model and log-rank test, stratified by age and high-risk cytogenetic abnormalities.
h. Operationalized as infections and infestations (SOC, severe AEs [CTCAE grade ≥ 3]).
i. Operationalized as haematological malignant tumours (sub-SMQ [narrow]), non-haematological malignant tumours (sub-SMQ [narrow]), haematological tumours of unspecified malignancy (sub-SMQ [narrow]), non-haematological tumours of unspecified malignancy (sub-SMQ [narrow]) and myelodysplastic syndrome (ad hoc PT). The following PTs were excluded: plasma cell leukaemia, plasma cell myeloma in remission, plasma cell leukaemia in remission, plasma cell myeloma, plasma cell myeloma recurrent, plasma cell myeloma refractory, and plasmacytoma.
j. Effect, CI: Cox proportional hazards model, p-value: log-rank test; both unstratified.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; DPd: daratumumab in combination with pomalidomide and dexamethasone; DVd: daratumumab in combination with bortezomib and dexamethasone; EORTC: European Organisation for Research and Treatment of Cancer; EPd: elotuzumab in combination with pomalidomide and dexamethasone; HR: hazard ratio; IRd: ixazomib in combination with lenalidomide and dexamethasone; Kd: carfilzomib in combination with dexamethasone; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

Table 18: Results (overall rates of side effects, dichotomous) – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 2: patients with ≥ 4 prior therapies)

Study Outcome category Outcome	Idecabtagene vicleucel		Individualized therapy selected from DPd, DVd, IRd, Kd or EPd		Idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
KarMMa-3					
Side effects[b]					
AEs (supplementary information)	79	78 (99)	41	41 (100)	–
SAEs	79	28 (35)	41	17 (41)	0.85 [0.53; 1.37]; 0.613
Severe AEs[c]	79	72 (91)	41	34 (83)	1.10 [0.94; 1.28]; 0.202
Discontinuation due to AE				ND	

a. Institute's calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [13]).
b. Based on analyses of events occurring up to 6 months after randomization.
c. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; DPd: daratumumab in combination with pomalidomide and dexamethasone; DVd: daratumumab in combination with bortezomib and dexamethasone; EORTC: European Organisation for Research and Treatment of Cancer; EPd: elotuzumab in combination with pomalidomide and dexamethasone; IRd: ixazomib in combination with lenalidomide and dexamethasone; Kd: carfilzomib in combination with dexamethasone; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

Due to the uncertainty in the implementation of the ACT (see Section 2.1.1) and due to the high risk of bias in some cases, no more than hints, for example of an added benefit, can be determined for all outcomes on the basis of the available information.

Mortality

Overall survival

No statistically significant difference between treatment groups was shown for the outcome of all-cause mortality. There is no hint of added benefit of idecabtagene vicleucel in comparison with individualized therapy selecting from DVd, DPd, IPd, Kd or EPd; an added benefit is therefore not proven.

Morbidity

Symptoms (recorded using EORTC QLQ-C30 and EORTC QLQ-MY20), health status (recorded using EQ-5D VAS)

No suitable data are available for symptoms (recorded using EORTC QLQ-C30 and EORTC QLQ-MY20) and health status (recorded using EQ-5D VAS), see Section 2.1.2 for reasons). In each case, there is no hint of added benefit of idecabtagene vicleucel in comparison with individualized therapy selecting from DVd, DPd, IPd, Kd or EPd; an added benefit is therefore not proven.

Health-related quality of life (recorded using EORTC QLQ-C30 and EORTC QLQ-MY20)

No suitable data are available for health-related quality of life (recorded using the EORTC QLQ-C30 and EORTC QLQ-MY20) (see Section 2.1.2 for reasons). In each case, there is no hint of added benefit of idecabtagene vicleucel in comparison with individualized therapy selecting from DVd, DPd, IPd, Kd or EPd; an added benefit is therefore not proven.

Side effects

SAEs and severe AEs

No statistically significant difference between treatment groups was shown for either of the outcomes of SAEs and severe AEs. In each case, there is no hint of greater or lesser harm of idecabtagene vicleucel in comparison with individualized therapy selecting from DVd, DPd, IPd, Kd or EPd; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

No suitable data are available for the outcome of discontinuation due to AEs (see Section 2.2.2.1 for reasons). There is no hint of greater or lesser harm of idecabtagene vicleucel in comparison with individualized therapy selecting from DVd, DPd, IPd, Kd or EPd; greater or lesser harm is therefore not proven.

Specific AEs

Cytokine release syndrome and infusion-related reactions

No suitable data are available for the outcomes of cytokine release syndrome and infusion-related reactions (see Section 2.2.2.1 for reasons). In each case, there is no hint of greater or lesser harm of idecabtagene vicleucel in comparison with individualized therapy selecting from DVd, DPd, IPd, Kd or EPd; greater or lesser harm is therefore not proven.

Severe neurological toxicity (CTCAE grade ≥ 3), severe infections (CTCAE grade ≥ 3), secondary malignancies (AEs)

No statistically significant difference between the treatment groups was shown for the outcomes of severe neurological toxicity (CTCAE grade ≥ 3), severe infections (CTCAE

grade ≥ 3), and secondary malignancies (AEs). For these outcomes, there is no hint of greater or lesser harm of idecabtagene vicleucel in comparison with individualized therapy selecting from DVd, DPd, IPd, Kd or EPd; greater or lesser harm is therefore not proven.

2.3.2.4 Subgroups and other effect modifiers

The following effect modifiers were considered to be relevant for the present benefit assessment:

- age (< 65 years/≥ 65 years)
- sex (female/male)
- R-ISS (I or II/III)

For the outcomes of overall survival and for the subsequently submitted analyses of the outcomes of SAEs and severe AEs (up to 6 months after randomization), the company did not present any subgroup analyses for the subpopulation relevant to research question 2. This approach is not appropriate but remains of no consequence in the present data situation.

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

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

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

2.3.3 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [14].

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

2.3.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.3.2.3 (see Table 19).

Table 19: Extent of added benefit at outcome level: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 2: patients with ≥ 4 prior therapies) (multipage table)

Outcome category **Outcome**	**Idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	31.0 vs. 23.4 months HR: 0.96 [0.57; 1.62]; p = 0.436	Lesser/added benefit not proven
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30, EORTC QLQ-MY20)	No suitable data[c]	Lesser/added benefit not proven
Health status (EQ-5D VAS)	No suitable data[c]	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30, EORTC QLQ-MY20	No suitable data[c]	Lesser/added benefit not proven
Side effects		
SAEs	35% vs. 41% RR: 0.85 [0.53; 1.37]; p = 0.613	Greater/lesser harm not proven
Severe AEs	91% vs. 83% RR: 1.10 [0.94; 1.28]; p = 0.202	Greater/lesser harm not proven
Discontinuation due to AEs	ND	Greater/lesser harm not proven
Cytokine release syndrome	No suitable data[d]	Greater/lesser harm not proven
Severe neurological toxicity	NA vs. NA HR: 0.39 [0.12; 1.28]; p = 0.106	Greater/lesser harm not proven
Infusion-related reactions	Outcome not recorded	Greater/lesser harm not proven
Severe infections	NA vs. NA HR: 0.98 [0.51; 1.88]; p = 0.951	Greater/lesser harm not proven
Secondary malignancies	NA vs. NA HR: 1.40 [0.37; 5.27]; p = 0.621	Greater/lesser harm not proven

Table 19: Extent of added benefit at outcome level: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 2: patients with ≥ 4 prior therapies) (multipage table)

Outcome category **Outcome**	**Idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
a. Probability provided if there is a statistically significant and relevant effect. b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u). c. No suitable data are available for this outcome; see Section 2.1.2 for reasons. d. No suitable data are available for this outcome; see Section 2.2.2.1 for reasons. AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; DPd: daratumumab in combination with pomalidomide and dexamethasone; DVd: daratumumab in combination with bortezomib and dexamethasone; EORTC: European Organisation for Research and Treatment of Cancer; EPd: elotuzumab in combination with pomalidomide and dexamethasone; HR. hazard ratio; IRd: ixazomib in combination with lenalidomide and dexamethasone; Kd: carfilzomib in combination with dexamethasone; NA: not achieved; ND: no data; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale		

2.3.3.2 Overall conclusion on added benefit

Table 20 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 20: Positive and negative effects from the assessment of idecabtagene vicleucel in comparison with individualized therapy (research question 2: patients with ≥ 4 prior therapies)

Positive effects	**Negative effects**
Outcomes with observation over the entire study duration	
–	–
Outcomes with shortened observation period	
–	–
No suitable data are available for the outcome categories of morbidity and health-related quality of life as well as for the outcomes of discontinuation due to AEs, cytokine release syndrome and infusion-related reactions.	
AE: adverse event	

Overall, neither positive nor negative effects were found for idecabtagene vicleucel in comparison with individualized therapy selecting from DPd, DVd, IPd, Kd or EPd. Therefore,

an added benefit of idecabtagene vicleucel in comparison with the ACT is not proven for patients with relapsed and refractory multiple myeloma who have received at least 4 prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.

2.4 Summary

The data subsequently submitted by the company in the commenting procedure do not change the conclusion drawn in dossier assessment A24-35 on the added benefit of idecabtagene vicleucel.

Table 21 below shows the result of the benefit assessment of idecabtagene vicleucel taking into account dossier assessment A24-35 and the present addendum.

Table 21: 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 21: 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 21: 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.

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Appendix A Kaplan-Meier curves

A.1 Research question 1: patients with 2 to 3 prior therapies

A.1.1 Mortality

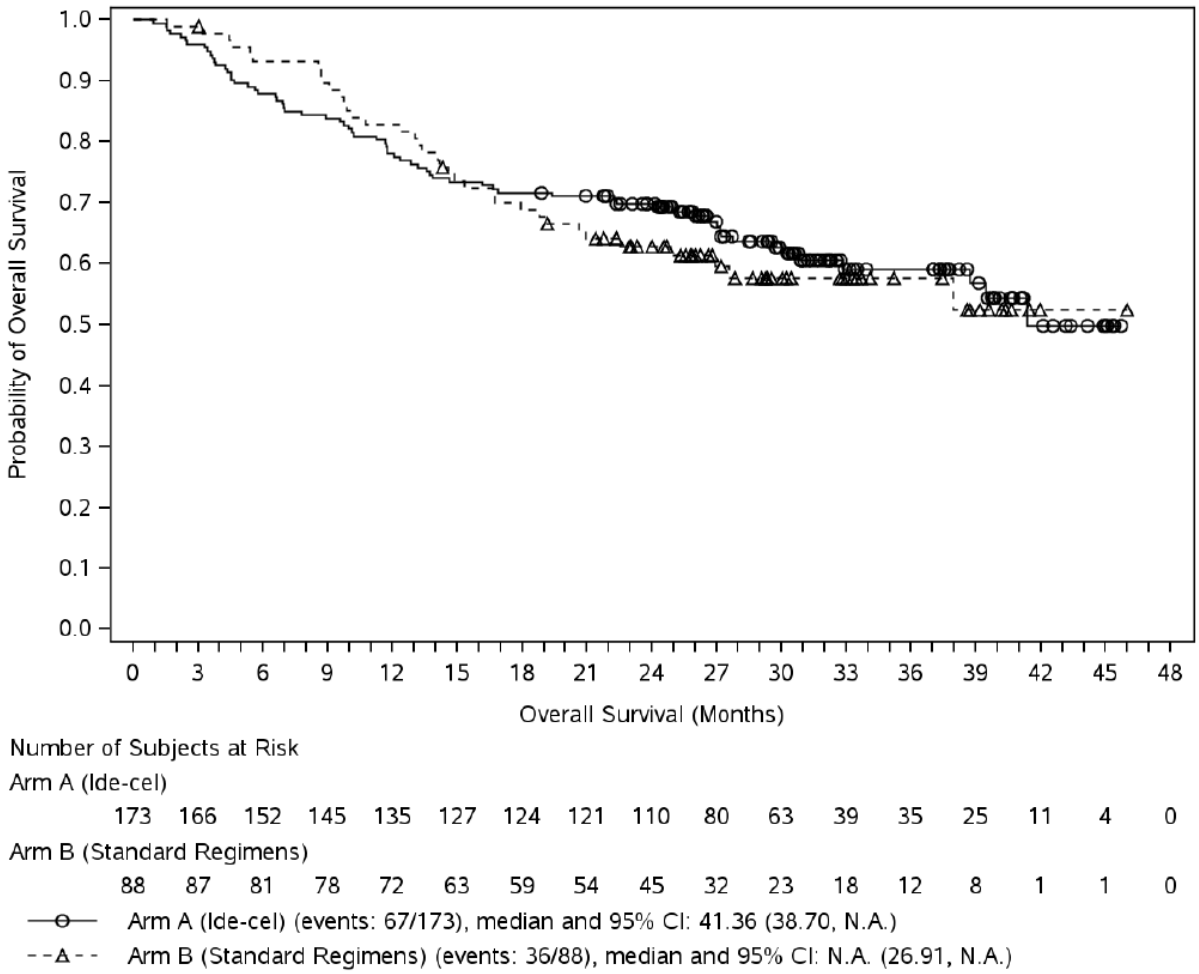

Figure 1: Kaplan-Meier curves for the outcome of overall survival, KarMMa-3 study, data cut-off: 28 April 2023, research question 1 (patients with 2 to 3 prior therapies)

A.1.2 Side effects

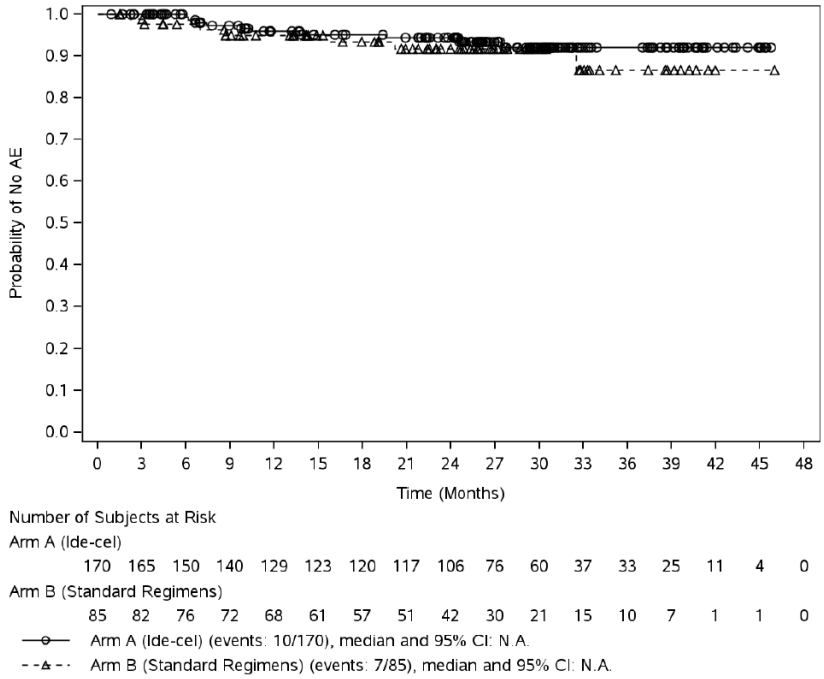

Figure 2: Kaplan-Meier curves for the outcome of secondary malignancies, KarMMa-3 study, data cut-off: 28 April 2023, research question 1 (patients with 2 to 3 prior therapies)

A.2 Research question 2: patients with at least 4 prior therapies

A.2.1 Mortality

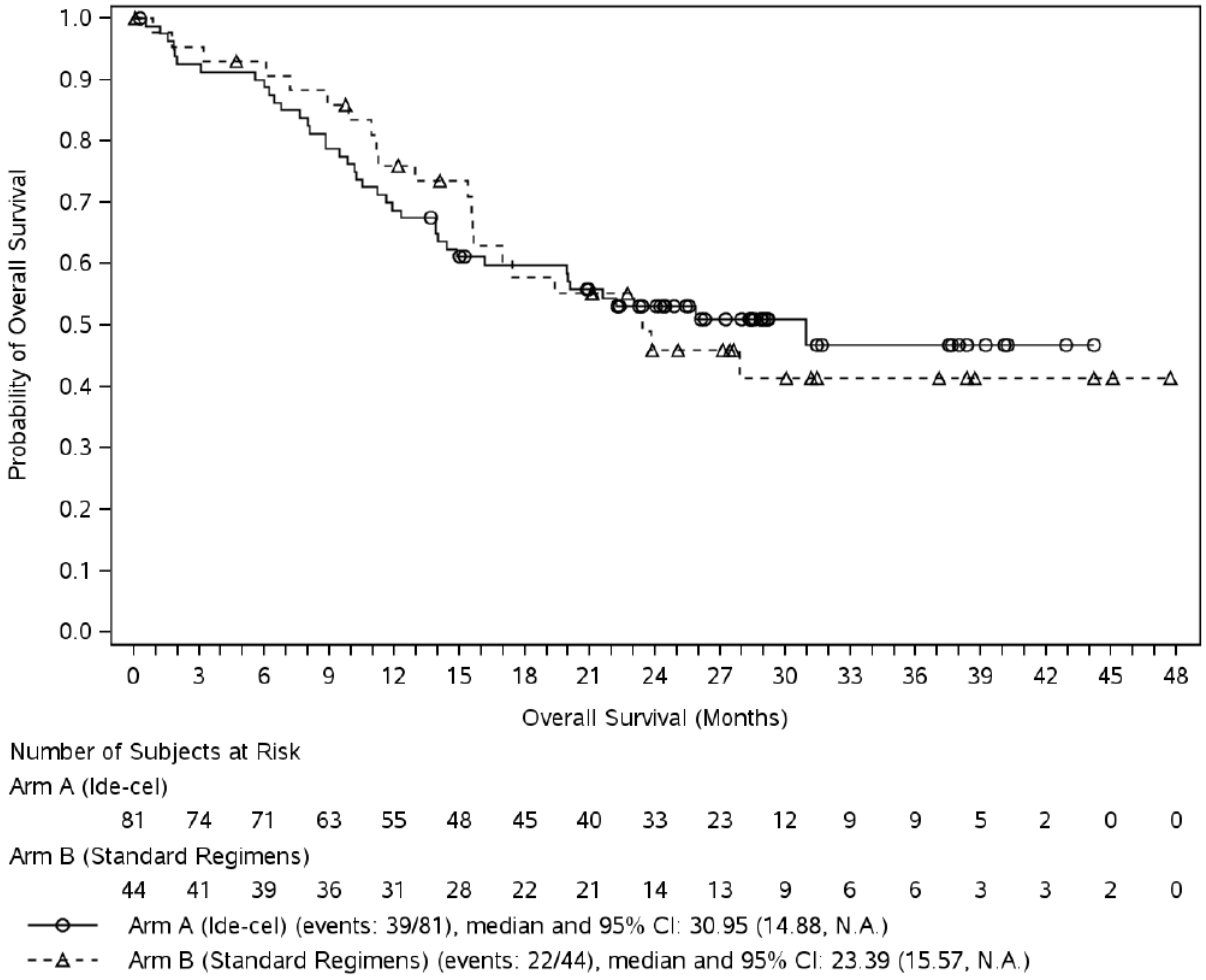

Figure 3: Kaplan-Meier curves for the outcome of overall survival, KarMMa-3 study, data cut-off: 28 April 2023, research question 2 (patients with ≥ 4 prior therapies)

A.2.2 Side effects

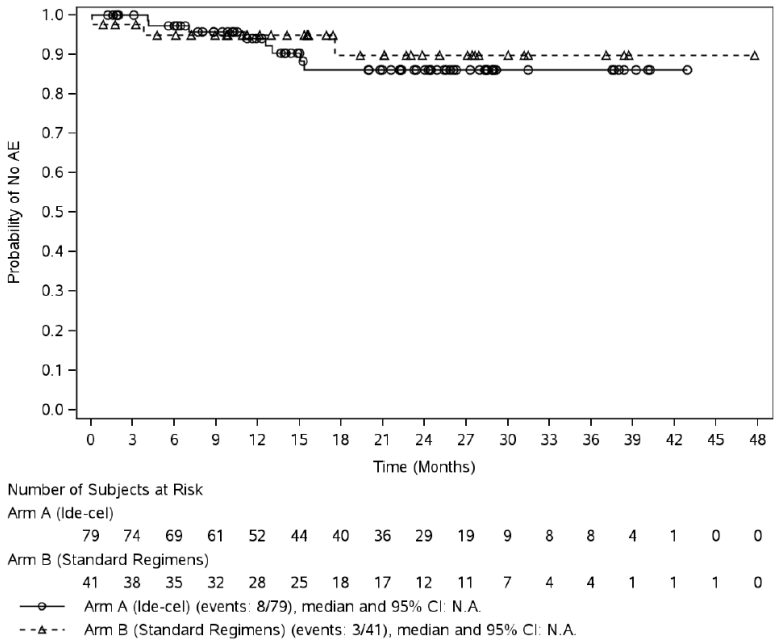

Figure 4: Kaplan-Meier curves for the outcome of secondary malignancies, KarMMa-3 study, data cut-off: 28 April 2023, research question 2 (patients with ≥ 4 prior therapies)

Appendix B Results on side effects

For the overall rates of AEs, SAEs, and severe AEs (CTCAE grade ≥ 3), the following tables present events for MedDRA SOCs and PTs, each on the basis of the following criteria:

- overall rate of AEs (irrespective of severity): events which occurred in at least 10% of patients in one study arm
- overall rates of severe AEs (CTCAE grade ≥ 3) and SAEs: events which occurred in at least 5% of patients in one study arm
- additionally, for all events irrespective of severity: events which occurred in at least 10 patients and in at least 1% of patients in one study arm

For the outcome of discontinuation due to AEs (SOC/PTs), no data are available for the respective subpopulations of research question 1 and research question 2.

B.1 Research question 1: patients with 2 to 3 prior therapies

Table 22: Common AEs[a, b] – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 1: patients with 2–3 prior therapies) (multipage table)

Study	Patients with event n (%)	
SOC[c] PT[c]	Idecabtagene vicleucel N[d] = 170	Individualized therapy selected from DPd, DVd, IRd, Kd or EPd N[d] = 85
KarMMa-3		
Overall AE rate	170 (100.0)	85 (100.0)
Blood and lymphatic system disorders	154 (90.6)	73 (85.9)
Neutropenia	139 (81.8)	65 (76.5)
Anaemia	111 (65.3)	51 (60.0)
Thrombocytopenia	101 (59.4)	49 (57.6)
Leukopenia	51 (30.0)	27 (31.8)
Lymphopenia	51 (30.0)	25 (29.4)
Febrile neutropenia	15 (8.8)	7 (8.2)
Immune system disorders	134 (78.8)	46 (54.1)
Cytokine release syndrome	132 (77.6)	46 (54.1)
Hypogammaglobulinaemia	12 (7.1)	6 (7.1)
Gastrointestinal disorders	131 (77.1)	66 (77.6)
Nausea	74 (43.5)	46 (54.1)
Diarrhoea	61 (35.9)	39 (45.9)
Constipation	44 (25.9)	17 (20.0)
Vomiting	31 (18.2)	19 (22.4)
Abdominal pain	10 (5.9)	11 (12.9)
General disorders and administration site conditions	116 (68.2)	67 (78.8)
Fatigue	47 (27.6)	36 (42.4)
Fever	49 (28.8)	28 (32.9)
Oedema peripheral	26 (15.3)	19 (22.4)
Asthenia	24 (14.1)	13 (15.3)
Chills	14 (8.2)	7 (8.2)
General physical health deterioration	10 (5.9)	4 (4.7)

Table 22: Common AEs[a, b] – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 1: patients with 2–3 prior therapies) (multipage table)

Study	**Patients with event n (%)**	
SOC[c] **PT[c]**	**Idecabtagene vicleucel N[d] = 170**	**Individualized therapy selected from DPd, DVd, IRd, Kd or EPd N[d] = 85**
Metabolism and nutrition disorders	118 (69.4)	58 (68.2)
Hypokalaemia	50 (29.4)	29 (34.1)
Hypophosphataemia	54 (31.8)	17 (20.0)
Hypomagnesaemia	38 (22.4)	14 (16.5)
Decreased appetite	37 (21.8)	22 (25.9)
Hypocalcaemia	34 (20.0)	16 (18.8)
Hyponatraemia	20 (11.8)	9 (10.6)
Hypertriglyceridaemia	17 (10.0)	6 (7.1)
Hypercalcaemia	13 (7.6)	3 (3.5)
Hypoalbuminaemia	10 (5.9)	2 (2.4)
Musculoskeletal and connective tissue disorders	107 (62.9)	56 (65.9)
Arthralgia	36 (21.2)	22 (25.9)
Back pain	31 (18.2)	20 (23.5)
Pain in extremity	22 (12.9)	19 (22.4)
Bone pain	17 (10.0)	8 (9.4)
Muscular weakness	10 (5.9)	10 (11.8)
Muscle spasms	10 (5.9)	12 (14.1)
Musculoskeletal chest pain	10 (5.9)	4 (4.7)
Infections and infestations	102 (60.0)	59 (69.4)
Upper respiratory tract infection	26 (15.3)	9 (10.6)
Pneumonia	21 (12.4)	9 (10.6)
COVID-19	11 (6.5)	12 (14.1)
Nervous system disorders	97 (57.1)	52 (61.2)
Headache	44 (25.9)	25 (29.4)
Neurotoxicity	19 (11.2)	12 (14.1)
Dizziness	22 (12.9)	11 (12.9)
Peripheral sensory neuropathy	7 (4.1)	14 (16.5)

Table 22: Common AEs[a, b] – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 1: patients with 2–3 prior therapies) (multipage table)

Study	**Patients with event n (%)**	
SOC[c] **PT[c]**	**Idecabtagene vicleucel N[d] = 170**	**Individualized therapy selected from DPd, DVd, IRd, Kd or EPd N[d] = 85**
Respiratory, thoracic and mediastinal disorders	87 (51.2)	55 (64.7)
Dyspnoea	31 (18.2)	28 (32.9)
Cough	28 (16.5)	18 (21.2)
Nasal congestion	15 (8.8)	6 (7.1)
Oropharyngeal pain	10 (5.9)	4 (4.7)
Hypoxia	10 (5.9)	3 (3.5)
Epistaxis	10 (5.9)	6 (7.1)
Pleural effusion	10 (5.9)	6 (7.1)
Rhinorrhoea	10 (5.9)	3 (3.5)
Investigations	67 (39.4)	38 (44.7)
Alanine aminotransferase increased	17 (10.0)	8 (9.4)
Aspartate aminotransferase increased	18 (10.6)	9 (10.6)
Gamma-glutamyltransferase increased	16 (9.4)	5 (5.9)
Blood alkaline phosphatase increased	12 (7.1)	5 (5.9)
C-reactive protein increased	12 (7.1)	3 (3.5)
Blood creatinine increased	13 (7.6)	7 (8.2)
Weight decreased	10 (5.9)	7 (8.2)
Vascular disorders	63 (37.1)	27 (31.8)
Hypertension	28 (16.5)	18 (21.2)
Hypotension	23 (13.5)	9 (10.6)
Skin and subcutaneous tissue disorders	52 (30.6)	34 (40.0)
Rash	12 (7.1)	7 (8.2)
Pruritus	12 (7.1)	10 (11.8)
Rash maculo-papular	4 (2.4)	9 (10.6)
Cardiac disorders	44 (25.9)	24 (28.2)
Tachycardia	17 (10.0)	8 (9.4)
Sinus tachycardia	10 (5.9)	5 (5.9)
Psychiatric disorders	42 (24.7)	30 (35.3)
Insomnia	28 (16.5)	15 (17.6)
Anxiety	12 (7.1)	7 (8.2)

Table 22: Common AEs[a, b] – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 1: patients with 2–3 prior therapies) (multipage table)

Study	**Patients with event n (%)**	
SOC[c] **PT[c]**	**Idecabtagene vicleucel N[d] = 170**	**Individualized therapy selected from DPd, DVd, IRd, Kd or EPd N[d] = 85**
Injury, poisoning and procedural complications	38 (22.4)	28 (32.9)
Fall	12 (7.1)	6 (7.1)
Renal and urinary disorders	39 (22.9)	19 (22.4)
Acute kidney injury	12 (7.1)	6 (7.1)
Eye disorders	21 (12.4)	15 (17.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	12 (7.1)	7 (8.2)
Hepatobiliary disorders	11 (6.5)	6 (7.1)

a. Events that occurred in ≥ 10 patients in the intervention arm, or in ≥ 10% of patients in the control arm.
b. Based on analyses of any events occurring within the first 6 months after the infusion of idecabtagene vicleucel or the first dose in the control arm, as well as severe AEs (CTCAE grade ≥ 3), SAEs and AEs of special interest occurring in the period from Month 7 to 28 days after progression. In addition, severe AEs (CTCAE grade ≥ 3), SAEs and AEs of special interest that occurred during follow-up observation and were attributed to the study medication by the investigator, as well as any AEs that occurred in the control arm within 3 months of the treatment switch, were included in the analyses.
c. Information taken from the comments of the company without adaptation.
d. Treated patients; in the comparator arm, patients continued to be analysed in the comparator arm in accordance with their randomization even after switching treatment.

AE: adverse event; COVID-19: coronavirus disease 2019; CTCAE: Common Terminology Criteria for Adverse Events; DPd: daratumumab in combination with pomalidomide and dexamethasone; DVd: daratumumab in combination with bortezomib and dexamethasone; EPd: elotuzumab in combination with pomalidomide and dexamethasone; IRd: ixazomib in combination with lenalidomide and dexamethasone; Kd: carfilzomib in combination with dexamethasone; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 23: Common SAEs[a, b] – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 1: patients with 2–3 prior therapies)

Study	**Patients with event n (%)**	
SOC[c] **PT[c]**	**Idecabtagene vicleucel N[d] = 170**	**Individualized therapy selected from DPd, DVd, IRd, Kd or EPd N[d] = 85**
KarMMa-3		
Overall SAE rate	91 (53.5)	52 (61.2)
Infections and infestations	40 (23.5)	22 (25.9)
Pneumonia	11 (6.5)	7 (8.2)
General disorders and administration site conditions	22 (12.9)	9 (10.6)
Blood and lymphatic system disorders	15 (8.8)	9 (10.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10 (5.9)	5 (5.9)
Nervous system disorders	14 (8.2)	7 (8.2)
Musculoskeletal and connective tissue disorders	11 (6.5)	12 (14.1)
Respiratory, thoracic and mediastinal disorders	10 (5.9)	12 (14.1)
Immune system disorders	11 (6.5)	0 (0)

a. Events that occurred in ≥ 5% of patients.
b. Based on analyses of any events occurring within the first 6 months after the infusion of idecabtagene vicleucel or the first dose in the control arm, as well as severe AEs (CTCAE grade ≥ 3), SAEs and AEs of special interest occurring in the period from Month 7 to 28 days after progression. In addition, severe AEs (CTCAE grade ≥ 3), SAEs and AEs of special interest that occurred during follow-up observation and were attributed to the study medication by the investigator, as well as any AEs that occurred in the control arm within 3 months of the treatment switch, were included in the analyses.
c. Information taken from the comments of the company without adaptation.
d. Treated patients; in the comparator arm, patients continued to be analysed in the comparator arm in accordance with their randomization even after switching treatment.

CTCAE: Common Terminology Criteria for Adverse Events; DPd: daratumumab in combination with pomalidomide and dexamethasone; DVd: daratumumab in combination with bortezomib and dexamethasone; EPd: elotuzumab in combination with pomalidomide and dexamethasone; IRd: ixazomib in combination with lenalidomide and dexamethasone; Kd: carfilzomib in combination with dexamethasone; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 24: Common severe AEs (CTCAE grade ≥ 3)[a, b] – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 1: patients with 2–3 prior therapies) (multipage table)

Study	**Patients with event n (%)**	
SOC[c] **PT[c]**	**Idecabtagene vicleucel N[d] = 170**	**Individualized therapy selected from DPd, DVd, IRd, Kd or EPd N[d] = 85**
KarMMa-3		
Overall rate of severe AEs (CTCAE grade ≥ 3)	161 (94.7)	80 (94.1)
Blood and lymphatic system disorders	150 (88.2)	72 (84.7)
Neutropenia	136 (80.0)	65 (76.5)
Anaemia	83 (48.8)	41 (48.2)
Thrombocytopenia	81 (47.6)	37 (43.5)
Leukopenia	50 (29.4)	27 (31.8)
Lymphopenia	48 (28.2)	24 (28.2)
Febrile neutropenia	15 (8.8)	6 (7.1)
Metabolism and nutrition disorders	59 (34.7)	20 (23.5)
Hypophosphataemia	34 (20.0)	6 (7.1)
Infections and infestations	39 (22.9)	22 (25.9)
Pneumonia	12 (7.1)	7 (8.2)
General disorders and administration site conditions	20 (11.8)	14 (16.5)
Investigations	18 (10.6)	12 (14.1)
Vascular disorders	19 (11.2)	13 (15.3)
Hypertension	17 (10.0)	12 (14.1)
Respiratory, thoracic and mediastinal disorders	16 (9.4)	10 (11.8)
Nervous system disorders	16 (9.4)	9 (10.6)
Musculoskeletal and connective tissue disorders	13 (7.6)	16 (18.8)
Renal and urinary disorders	11 (6.5)	6 (7.1)
Immune system disorders	13 (7.6)	1 (1.2)
Cytokine release syndrome	10 (5.9)	0 (0)
Cardiac disorders	9 (5.3)	10 (11.8)

a. Events that occurred in ≥ 5% of patients.
b. Based on analyses of any events occurring within the first 6 months after the infusion of idecabtagene vicleucel or the first dose in the control arm, as well as severe AEs (CTCAE grade ≥ 3), SAEs and AEs of special interest occurring in the period from Month 7 to 28 days after progression. In addition, severe AEs (CTCAE grade ≥ 3), SAEs and AEs of special interest that occurred during follow-up observation and were attributed to the study medication by the investigator, as well as any AEs that occurred in the control arm within 3 months of the treatment switch, were included in the analyses.
c. Information taken from the comments of the company without adaptation.
d. Treated patients; in the comparator arm, patients continued to be analysed in the comparator arm in accordance with their randomization even after switching treatment.

Table 24: Common severe AEs (CTCAE grade ≥ 3)[a, b] – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 1: patients with 2–3 prior therapies) (multipage table)

Study	**Patients with event n (%)**	
SOC[c] **PT[c]**	**Idecabtagene vicleucel N[d] = 170**	**Individualized therapy selected from DPd, DVd, IRd, Kd or EPd N[d] = 85**
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; DPd: daratumumab in combination with pomalidomide and dexamethasone; DVd: daratumumab in combination with bortezomib and dexamethasone; EPd: elotuzumab in combination with pomalidomide and dexamethasone; IRd: ixazomib in combination with lenalidomide and dexamethasone; Kd: carfilzomib in combination with dexamethasone; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class		

B.2 Research question 2: patients with at least 4 prior therapies

Table 25: Common AEs[a, b] – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 2: patients with 4 prior therapies) (multipage table)

Study	**Patients with event n (%)**	
SOC[c] **PT[c]**	**Idecabtagene vicleucel** **N[d] = 79**	**Individualized therapy selected from DPd, DVd, IRd, Kd or EPd** **N[d] = 41**
KarMMa-3		
Overall AE rate	78 (98.7)	41 (100.0)
Blood and lymphatic system disorders	71 (89.9)	38 (92.7)
Neutropenia	57 (72.2)	26 (63.4)
Anaemia	54 (68.4)	24 (58.5)
Thrombocytopenia	37 (46.8)	19 (46.3)
Leukopenia	23 (29.1)	11 (26.8)
Lymphopenia	23 (29.1)	12 (29.3)
Immune system disorders	68 (86.1)	21 (51.2)
Cytokine release syndrome	65 (82.3)	19 (46.3)
Hypogammaglobulinaemia	10 (12.7)	5 (12.2)
Gastrointestinal disorders	53 (67.1)	28 (68.3)
Nausea	39 (49.4)	20 (48.8)
Diarrhoea	25 (31.6)	12 (29.3)
Constipation	24 (30.4)	7 (17.1)
Vomiting	19 (24.1)	7 (17.1)
General disorders and administration site conditions	53 (67.1)	32 (78.0)
Fatigue	23 (29.1)	18 (43.9)
Fever	19 (24.1)	11 (26.8)
Oedema peripheral	12 (15.2)	9 (22.0)
Chills	9 (11.4)	2 (4.9)
General physical health deterioration	9 (11.4)	2 (4.9)

Table 25: Common AEs[a, b] – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 2: patients with 4 prior therapies) (multipage table)

Study	**Patients with event n (%)**	
SOC[c] **PT[c]**	**Idecabtagene vicleucel N[d] = 79**	**Individualized therapy selected from DPd, DVd, IRd, Kd or EPd N[d] = 41**
Metabolism and nutrition disorders	51 (64.6)	29 (70.7)
Hypokalaemia	30 (38.0)	10 (24.4)
Hypophosphataemia	25 (31.6)	11 (26.8)
Hypomagnesaemia	14 (17.7)	9 (22.0)
Decreased appetite	13 (16.5)	9 (22.0)
Hypocalcaemia	12 (15.2)	6 (14.6)
Hypertriglyceridaemia	6 (7.6)	6 (14.6)
Hypercalcaemia	8 (10.1)	5 (12.2)
Hypoalbuminaemia	2 (2.5)	5 (12.2)
Musculoskeletal and connective tissue disorders	50 (63.3)	25 (61.0)
Arthralgia	15 (19.0)	10 (24.4)
Back pain	17 (21.5)	6 (14.6)
Pain in extremity	11 (13.9)	7 (17.1)
Myalgia	9 (11.4)	2 (4.9)
Muscular weakness	7 (8.9)	5 (12.2)
Muscle spasms	2 (2.5)	6 (14.6)
Musculoskeletal chest pain	2 (2.5)	6 (14.6)
Infections and infestations	49 (62.0)	29 (70.7)
COVID-19	5 (6.3)	5 (12.2)
Nervous system disorders	46 (58.2)	27 (65.9)
Headache	15 (19.0)	14 (34.1)
Neurotoxicity	15 (19.0)	3 (7.3)
Dizziness	6 (7.6)	6 (14.6)
Peripheral sensory neuropathy	6 (7.6)	7 (17.1)
Respiratory, thoracic and mediastinal disorders	34 (43.0)	22 (53.7)
Dyspnoea	13 (16.5)	8 (19.5)
Cough	11 (13.9)	8 (19.5)
Investigations	35 (44.3)	23 (56.1)
Aspartate aminotransferase increased	4 (5.1)	6 (14.6)
Weight decreased	9 (11.4)	5 (12.2)
Blood creatinine increased	2 (2.5)	5 (12.2)

Table 25: Common AEs[a, b] – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 2: patients with 4 prior therapies) (multipage table)

Study	**Patients with event n (%)**	
SOC[c] **PT[c]**	**Idecabtagene vicleucel N[d] = 79**	**Individualized therapy selected from DPd, DVd, IRd, Kd or EPd N[d] = 41**
Vascular disorders	28 (35.4)	16 (39.0)
Hypertension	13 (16.5)	10 (24.4)
Hypotension	14 (17.7)	7 (17.1)
Skin and subcutaneous tissue disorders	22 (27.8)	12 (29.3)
Cardiac disorders	22 (27.8)	10 (24.4)
Tachycardia	8 (10.1)	1 (2.4)
Psychiatric disorders	19 (24.1)	17 (41.5)
Insomnia	12 (15.2)	13 (31.7)
Injury, poisoning and procedural complications	17 (21.5)	13 (31.7)
Renal and urinary disorders	15 (19.0)	5 (12.2)
Eye disorders	9 (11.4)	10 (24.4)
Vision blurred	2 (2.5)	5 (12.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9 (11.4)	3 (7.3)

a. Events that occurred in ≥ 10% of patients.
b. Based on analyses of any events occurring within the first 6 months after the infusion of idecabtagene vicleucel or the first dose in the control arm, as well as severe AEs (CTCAE grade ≥ 3), SAEs and AEs of special interest occurring in the period from Month 7 to 28 days after progression. In addition, severe AEs (CTCAE grade ≥ 3), SAEs and AEs of special interest that occurred during follow-up observation and were attributed to the study medication by the investigator, as well as any AEs that occurred in the control arm within 3 months of the treatment switch, were included in the analyses.
c. Information taken from the comments of the company without adaptation.
d. Treated patients; in the comparator arm, patients continued to be analysed in the comparator arm in accordance with their randomization even after switching treatment.

AE: adverse event; COVID-19: coronavirus disease 2019; CTCAE: Common Terminology Criteria for Adverse Events; DPd: daratumumab in combination with pomalidomide and dexamethasone; DVd: daratumumab in combination with bortezomib and dexamethasone; EPd: elotuzumab in combination with pomalidomide and dexamethasone; IRd: ixazomib in combination with lenalidomide and dexamethasone; Kd: carfilzomib in combination with dexamethasone; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 26: Common SAEs[a, b] – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 2: patients with 4 prior therapies)

Study	**Patients with event n (%)**	
SOC[c] **PT[c]**	**Idecabtagene vicleucel N[d] = 79**	**Individualized therapy selected from DPd, DVd, IRd, Kd or EPd N[d] = 41**
KarMMa-3		
Overall SAE rate	48 (60.8)	26 (63.4)
Infections and infestations	27 (34.2)	14 (34.1)
General disorders and administration site conditions	12 (15.2)	6 (14.6)
General physical health deterioration	9 (11.4)	2 (4.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9 (11.4)	3 (7.3)

a. Events that occurred in ≥ 5% of patients.
b. Based on analyses of any events occurring within the first 6 months after the infusion of idecabtagene vicleucel or the first dose in the control arm, as well as severe AEs (CTCAE grade ≥ 3), SAEs and AEs of special interest occurring in the period from Month 7 to 28 days after progression. In addition, severe AEs (CTCAE grade ≥ 3), SAEs and AEs of special interest that occurred during follow-up observation and were attributed to the study medication by the investigator, as well as any AEs that occurred in the control arm within 3 months of the treatment switch, were included in the analyses.
c. Information taken from the comments of the company without adaptation.
d. Treated patients; in the comparator arm, patients continued to be analysed in the comparator arm in accordance with their randomization even after switching treatment.

CTCAE: Common Terminology Criteria for Adverse Events; DPd: daratumumab in combination with pomalidomide and dexamethasone; DVd: daratumumab in combination with bortezomib and dexamethasone; EPd: elotuzumab in combination with pomalidomide and dexamethasone; IRd: ixazomib in combination with lenalidomide and dexamethasone; Kd: carfilzomib in combination with dexamethasone; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 27: Common severe AEs (CTCAE grade ≥ 3)[a, b] – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 2: patients with 4 prior therapies)

Study	Patients with event n (%)	
SOC[c] **PT[c]**	**Idecabtagene vicleucel N[d] = 79**	**Individualized therapy selected from DPd, DVd, IRd, Kd or EPd N[d] = 41**
KarMMa-3		
Overall rate of severe AEs (CTCAE grade ≥ 3)	75 (94.9)	40 (97.6)
Blood and lymphatic system disorders	69 (87.3)	37 (90.2)
Neutropenia	54 (68.4)	26 (63.4)
Anaemia	44 (55.7)	18 (43.9)
Thrombocytopenia	27 (34.2)	16 (39.0)
Leukopenia	23 (29.1)	9 (22.0)
Lymphopenia	23 (29.1)	12 (29.3)
Metabolism and nutrition disorders	31 (39.2)	15 (36.6)
Hypophosphataemia	16 (20.3)	6 (14.6)
Infections and infestations	27 (34.2)	14 (34.1)
General disorders and administration site conditions	13 (16.5)	7 (17.1)
General physical health deterioration	9 (11.4)	2 (4.9)
Investigations	12 (15.2)	7 (17.1)
Vascular disorders	10 (12.7)	4 (9.8)
Nervous system disorders	5 (6.3)	6 (14.6)

a. Events that occurred in ≥ 5% of patients.
b. Based on analyses of any events occurring within the first 6 months after the infusion of idecabtagene vicleucel or the first dose in the control arm, as well as severe AEs (CTCAE grade ≥ 3), SAEs and AEs of special interest occurring in the period from Month 7 to 28 days after progression. In addition, severe AEs (CTCAE grade ≥ 3), SAEs and AEs of special interest that occurred during follow-up observation and were attributed to the study medication by the investigator, as well as any AEs that occurred in the control arm within 3 months of the treatment switch, were included in the analyses.
c. Information taken from the comments of the company without adaptation.
d. Treated patients; in the comparator arm, patients continued to be analysed in the comparator arm in accordance with their randomization even after switching treatment.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; DPd: daratumumab in combination with pomalidomide and dexamethasone; DVd: daratumumab in combination with bortezomib and dexamethasone; EPd: elotuzumab in combination with pomalidomide and dexamethasone; IRd: ixazomib in combination with lenalidomide and dexamethasone; Kd: carfilzomib in combination with dexamethasone; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Appendix C Supplementary presentation of results on side effects (censoring at 6 months or at progression, whichever occurred later)

C.1 Research question 1: patients with 2 to 3 prior therapies

Table 28: Results (side effects, time to event) – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 1: patients with 2–3 prior therapies)

Study Outcome category Outcome	Idecabtagene vicleucel		Individualized therapy selected from DPd, DVd, IRd, Kd or EPd		Idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
KarMMa-3					
Side effects[b]					
AEs	170	0.4 [0.3; 0.6] 170 (100)	85	0.3 [0.2; 0.3] 85 (100)	–
SAEs	170	9.0 [5.1; 23.4] 91 (54)	85	7.3 [5.4; 9.4] 52 (61)	0.87 [0.62; 1.22]; 0.423
Severe AEs[c]	170	1.4 [1.3; 1.6] 161 (95)	85	1.5 [1.0; 2.4] 80 (94)	1.42 [1.08; 1.87]; 0.013
Discontinuation due to AEs				ND	

a. Effect, CI: Cox proportional hazards model, p-value: log-rank test; both unstratified.
b. Based on analyses with censoring 6 months after randomization or 28 days after progression/end of treatment, whichever occurs later.
c. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; DPd: daratumumab in combination with pomalidomide and dexamethasone; DVd: daratumumab in combination with bortezomib and dexamethasone; EPd: elotuzumab in combination with pomalidomide and dexamethasone; HR: hazard ratio; IRd: ixazomib in combination with lenalidomide and dexamethasone; Kd: carfilzomib in combination with dexamethasone; n: number of patients with (at least one) event; N: number of analysed patients; NC: not calculable; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event

C.2 Research question 2: patients with at least 4 prior therapies

Table 29: Results (side effects, time to event) – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (research question 2: patients with ≥ 4 prior therapies)

Study Outcome category Outcome	Idecabtagene vicleucel		Individualized therapy selected from DPd, DVd, IRd, Kd or EPd		Idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
KarMMa-3					
Side effects[b]					
AEs	79	0.3 [0.2; 0.4] 78 (99)	41	0.3 [0.2; 0.5] 41 (100)	–
SAEs	79	7.8 [6.3; 13.4] 47 (60)	41	8.5 [5.1; 12.9] 26 (63)	0.96 [0.59; 1.55]; 0.856
Severe AEs[c]	79	1.6 [1.4; 1.8] 74 [94]	41	1.4 [1.0; 2.6] 40 (98)	1.36 [0.90; 2.04]; 0.154
Discontinuation due to AEs				ND	

a. Effect, CI: Cox proportional hazards model, p-value: log-rank test; both unstratified.
b. Based on analyses with censoring 6 months after randomization or 28 days after progression/end of treatment, whichever occurs later.
c. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; DPd: daratumumab in combination with pomalidomide and dexamethasone; DVd: daratumumab in combination with bortezomib and dexamethasone; EPd: elotuzumab in combination with pomalidomide and dexamethasone; HR: hazard ratio; IRd: ixazomib in combination with lenalidomide and dexamethasone; Kd: carfilzomib in combination with dexamethasone; n: number of patients with (at least one) event; N: number of analysed patients; NC: not calculable; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event

Appendix D Kaplan-Meier curves for the supplementary presentation of results on side effects (censoring at 6 months or at progression, whichever occurred later)

D.1 Research question 1: patients with 2 to 3 prior therapies

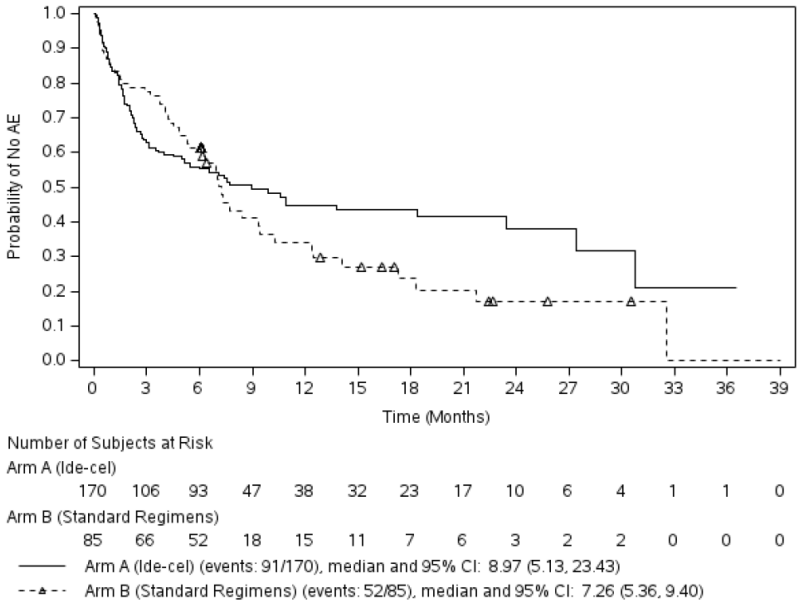

Figure 5: Kaplan-Meier curves for the outcome of SAEs, KarMMa-3 study, data cut-off: 28 April 2023, research question 1 (patients with 2 to 3 prior therapies)

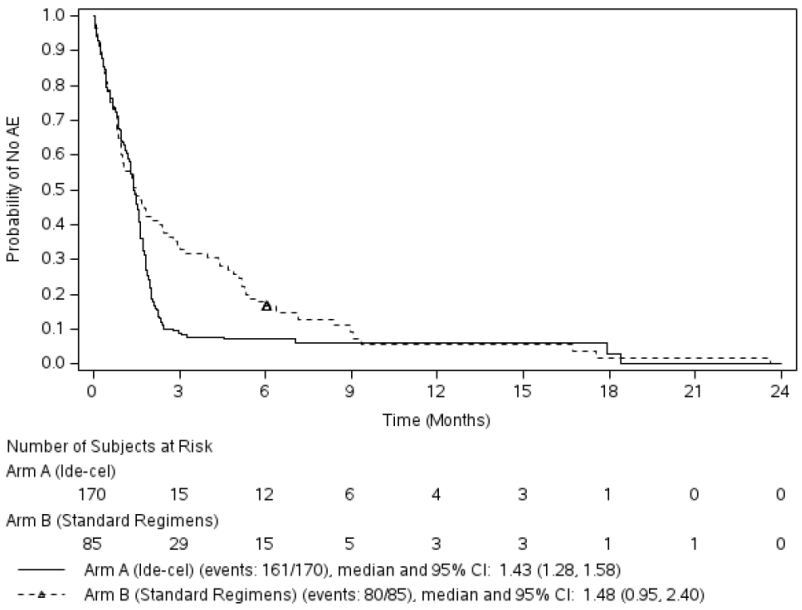

Figure 6: Kaplan-Meier curves for the outcome of severe AEs (CTCAE grade ≥ 3), KarMMa-3 study, data cut-off: 28 April 2023, research question 1 (patients with 2 to 3 prior therapies)

D.2 Research question 2: patients with at least 4 prior therapies

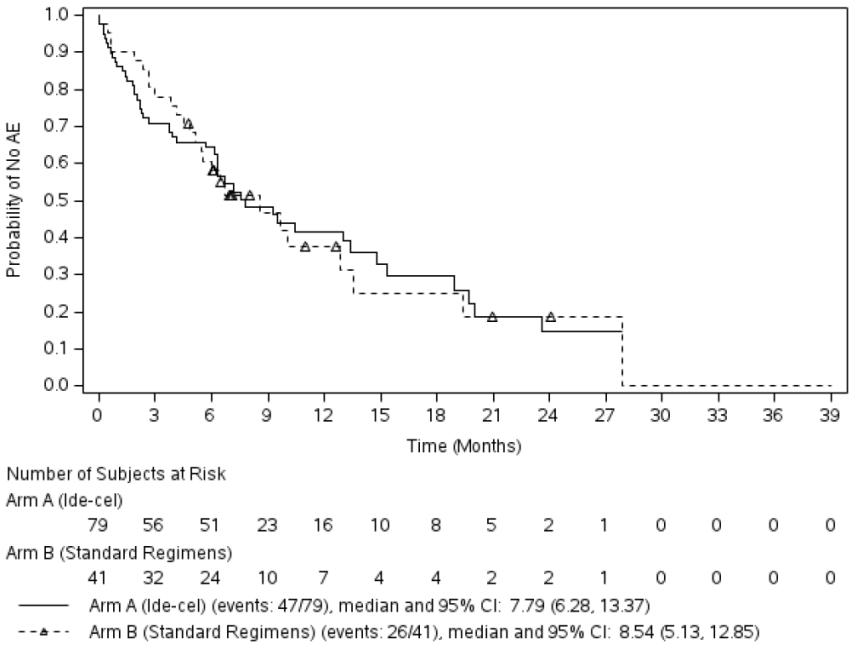

Figure 7: Kaplan-Meier curves for the outcome of SAEs, KarMMa-3 study, data cut-off: 28 April 2023, research question 2 (patients with ≥ 4 prior therapies)

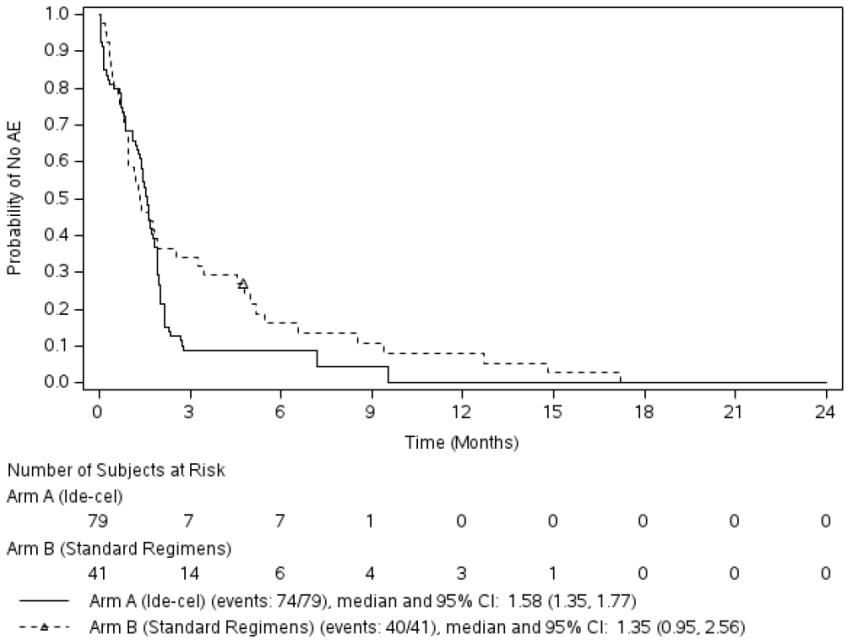

Figure 8: Kaplan-Meier curves for the outcome of severe AEs (CTCAE grade ≥ 3), KarMMa-3 study, data cut-off: 28 April 2023, research question 2 (patients with ≥ 4 prior therapies)

Appendix E Supplementary presentation of patient characteristics and results for the total population of the KarMMa-3 study

E.1 Study characteristics

A detailed description of the KarMMa-3 study can be found in dossier assessment A24-35 [1]. The tables below only present the patient characteristics, subsequent therapies and information on the course of the study for the total population of the KarMMa-3 study.

Patient characteristics

Table 30 shows the characteristics of the patients in the KarMMa-3 study.

Table 30: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (total population) (multipage table)

Study Characteristic Category	Idecabtagene vicleucel N[a] = 254	Individualized therapy selected from DPd, DVd, IRd, Kd or EPd N[a] = 132
KarMMa-3		
Age [years]		
Mean (SD)	62 (9)	61 (9)
Age group, n (%)		
< 65 years	150 (59)	78 (59)
≥ 65 years	104 (41)	54 (41)
Sex [F/M], %	39/61	40/60
Family origin, n (%)		
Native American or Alaska Native	1 (< 1)	0 (0)
Asian	7 (3)	5 (4)
Black or African American	18 (7)	18 (14)
White	172 (68)	78 (59)
Not reported	54 (21)	27 (21)
Other	2 (< 1)	3 (2)
ECOG PS, n (%)		
0	120 (47)	66 (50)
1	133 (52)	62 (47)
≥ 2	1 (< 1)	4 (3)[b]
Time since first diagnosis [years]		
Mean (SD)	4.7 (2.9)	5.1 (3.1)
Median (Q1; Q3)	4.1 (2.8; 5.8)	4.0 (3.0; 6.9)

Table 30: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (total population) (multipage table)

Study Characteristic Category	**Idecabtagene vicleucel N[a] = 254**	**Individualized therapy selected from DPd, DVd, IRd, Kd or EPd N[a] = 132**
Revised ISS stage, n (%)		
Stage I	50 (20)	26 (20)
Stage II	150 (59)	82 (62)
Stage III	31 (12)	14 (11)
Unknown or not reported	23 (9)	10 (8)
Cytogenetic risk group, n (%)		
High risk	107 (42)	61 (46)
del(17p)	66 (26)	42 (32)
t(4;14)	43 (17)	18 (14)
t(14;16)	8 (3)	4 (3)
Non-high risk	114 (45)	55 (42)
Unknown or not reported	33 (13)	16 (12)
Prior radiation therapy for multiple myeloma, n (%)	90 (35)	46 (35)
Prior surgery for multiple myeloma, n (%)	19 (8)	10 (8)
Prior autologous stem cell transplant, n (%)	214 (84)	114 (86)
1 transplant	167 (66)	87 (66)
> 1 transplant	47 (19)	27 (21)
Number of prior anti-myeloma regimens, n (%)		
2	78 (31)	39 (30)
3	95 (37)	49 (37)
4	81 (32)	44 (33)
Refractory status, n (%)		
IMiD	224 (88)	124 (94)
Lenalidomide	186 (73)	104 (79)
Pomalidomide	127 (50)	70 (53)
Thalidomide	10 (4)	2 (2)
Proteasome inhibitor	189 (74)	95 (72)
Bortezomib	112 (44)	60 (46)
Carfilzomib	104 (41)	43 (33)
Ixazomib/ixazomib citrate	35 (14)	23 (17)
Anti-CD38 antibodies	242 (95)	124 (94)
Daratumumab	242 (95)	123 (93)
Isatuximab	1 (< 1)	1 (< 1)

Table 30: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (total population) (multipage table)

Study Characteristic Category	**Idecabtagene vicleucel N[a] = 254**	**Individualized therapy selected from DPd, DVd, IRd, Kd or EPd N[a] = 132**
Other	24 (9)	20 (15)
Elotuzumab	18 (7)	16 (12)
Selinexor	3 (1)	3 (2)
Panobinostat	3 (1)	1 (< 1)
Double-refractory (IMiD and PI), n (%)	169 (67)	91 (69)
Triple-refractory (IMiD, PI, anti-CD38 antibodies), n (%)	164 (65)	89 (67)
Penta-refractory, n (%)	15 (6)	5 (4)
Bone lesions, n (%)		
Yes	194 (76)	104 (79)
No	59 (23)	28 (21)
Unknown or not reported	1 (< 1)	0 (0)
Myeloma type, n (%)		
IgA	50 (20)	22 (17)
IgD	0 (0)	2 (2)
IgG	166 (65)	89 (67)
IgM	1 (< 1)	0 (0)
Not confirmed	37 (15)	18 (14)
Missing/unknown	0 (0)	1 (< 1)
Light chain disease, n (%)	34 (13)	16 (12)
Treatment discontinuation, n (%)	0 (0)[c]	119 (94.4)[d]
Study discontinuation, n (%)[e]	118 (46.5[b])	38 (28.8[b])

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Institute's calculation.
c. 24 patients (9.4%) received leukapheresis but did not receive idecabtagene vicleucel.
d. Common reasons for treatment discontinuation in the control arm were disease progression (106 patients) and withdrawal of consent (7 patients).
e. Common reasons for study discontinuation in the intervention vs. control arm were death (94 vs. 25 patients) and withdrawal of consent (23 vs. 13 patients).

Table 30: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (total population) (multipage table)

Study Characteristic Category	Idecabtagene vicleucel N[a] = 254	Individualized therapy selected from DPd, DVd, IRd, Kd or EPd N[a] = 132
CD: cluster of differentiation; DPd: daratumumab in combination with pomalidomide and dexamethasone; DVd: daratumumab in combination with bortezomib und dexamethasone; ECOG PS: Eastern Cooperative Oncology Group Performances Status; EPd: elotuzumab in combination with pomalidomide and dexamethasone; F: female; IgA: immunoglobulin A; IgD: immunoglobulin D; IgE: immunoglobulin E; IgG: immunoglobulin G; IgM: immunoglobulin M; IMiD: immunomodulatory drugs; IRd: ixazomib in combination with lenalidomide and dexamethasone; ISS: International Staging System; Kd: carfilzomib in combination with dexamethasone; M: male; n: number of patients in the category; N: number of randomized patients; PI: proteasome inhibitor; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation		

Information on the course of the study

Table 31 shows patients' median treatment duration and the median observation period for individual outcomes and outcome categories.

Table 31: Information on the course of the study – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (total population)

Study **Duration of the study phase** **Outcome category/outcome**	**Idecabtagene vicleucel** **N[a] = 254**	**Individualized therapy selected from DPd, DVd, IRd, Kd or EPd** **N[a] = 132**
KarMMa-3		
Treatment duration [months] (data cut-off 18 April 2022)		
Median [Q1; Q3]	ND	DPd: 5.8 [2.7; 15.0][b] DVd: 2.8 [0.5; 5.6][b] IRd: 3.9 [2.0; 5.5][b] Kd: 5.8 [1.9; 12.0][b] EPd: 3.9 [1.6; 6.4][b]
Mean (SD)	ND	DPd: 10.2 (9.4)[b] DVd: 3.0 (2.5)[b] IRd: 5.0 (4.7)[b] Kd: 7.6 (5.8)[b] EPd: 4.6 (3.6)[b]
Observation period [months]		
Overall survival		
Median [min; max]	ND	ND
Mean (SD)	ND	ND
Morbidity, health-related quality of life		
EORTC QLQ-C30, EORTC QLQ-MY20, EQ-5D VAS	No suitable data[c]	
Side effects[d]	ND	ND

a. Number of randomized patients.
b. Institute's calculation.
c. See Section 2.1.2 for an explanation.
d. For the outcomes of SAEs and severe AEs, the analyses of events up to 6 months after randomization subsequently submitted by the company are considered for the benefit assessment. For the specific AEs, the subsequently submitted analyses in accordance with Module 4 B are considered (see also Section 2.1.3).

DPd: daratumumab in combination with pomalidomide and dexamethasone; DVd: daratumumab in combination with bortezomib and dexamethasone; EORTC: European Organisation for Research and Treatment of Cancer; EPd: elotuzumab in combination with pomalidomide and dexamethasone; IRd: ixazomib in combination with lenalidomide and dexamethasone; Kd: carfilzomib in combination with dexamethasone; max: maximum; min: minimum; N: number of analysed patients; ND: no data; Q1: first quartile; Q3: third quartile; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

Subsequent therapies

Table 32 shows for the total population which subsequent therapies patients received after discontinuing the study medication.

Table 32: Information on subsequent anti-multiple myeloma therapies (≥ 2 patients in ≥ 1 treatment arm) – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (total population) (multipage table)

Study **Drug class** **Drug**	**Patients with subsequent therapy, n (%)**	
	Idecabtagene vicleucel **N = 254**	**Individualized therapy selected from DPd, DVd, IRd, Kd or EPd** **N = 132**
KarMMa-3 (data cut-off 28 April 2023)		
Total	146 (57.5)	104 (78.8)
Antineoplastic and immunomodulatory drugs	146 (100.0[a])	103 (99.0[a])
Cyclophosphamide	57 (39.0[a])	60 (57.7[a])
Carfilzomib	60 (41.1[a])	53 (51.0[a])
Pomalidomide	58 (39.7[a])	23 (22.1[a])
Idecabtagene vicleucel	0 (0[a])	70 (67.3[a])
Bortezomib	33 (22.6[a])	23 (22.1[a])
Etoposide	22 (15.1[a])	24 (23.1[a])
Daratumumab	26 (17.8[a])	17 (16.3[a])
Belantamab mafodotin	25 (17.1[a])	14 (13.5[a])
Cisplatin	19 (13.0[a])	18 (17.3[a])
Selinexor	24 (16.4[a])	9 (8.7[a])
Doxorubicin	14 (9.6[a])	18 (17.3[a])
Elotuzumab	17 (11.6[a])	6 (5.8[a])
Investigational antineoplastic drugs	17 (11.6[a])	2 (1.9[a])
Isatuximab	12 (8.2[a])	7 (6.7[a])
Teclistamab	15 (10.3[a])	4 (3.8[a])
Elranatamab	13 (8.9[a])	5 (4.8[a])
Fludarabine	4 (2.7[a])	13 (12.5[a])
Talquetamab	10 (6.8[a])	6 (5.8[a])
Lenalidomide	6 (4.1[a])	9 (8.7[a])
Melphalan	8 (5.5[a])	7 (6.7[a])
Cevostamab	11 (7.5[a])	3 (2.9[a])
Bendamustine	3 (2.1[a])	7 (6.7[a])
Ixazomib	4 (2.7[a])	6 (5.8[a])
Venetoclax	5 (3.4[a])	3 (2.9[a])
Thalidomide	2 (1.4[a])	4 (3.8[a])
Carmustine	3 (2.1[a])	1 (< 1[a])
Ciltacabtagene autoleucel	3 (2.1[a])	1 (< 1[a])
Cytarabine	3 (2.1[a])	1 (< 1[a])
Daratumumab hyaluronidase fihj	4 (2.7[a])	0 (0[a])
Iberdomide	4 (2.7[a])	0 (0[a])
Melphalan flufenamide	3 (2.1[a])	0 (0[a])

Table 32: Information on subsequent anti-multiple myeloma therapies (≥ 2 patients in ≥ 1 treatment arm) – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (total population) (multipage table)

Study **Drug class** **Drug**	**Patients with subsequent therapy, n (%)**	
	Idecabtagene vicleucel **N = 254**	**Individualized therapy selected from DPd, DVd, IRd, Kd or EPd** **N = 132**
Pembrolizumab	3 (2.1[a])	0 (0[a])
Systemic hormonal preparations, excl. sex hormones and insulins	114 (78.1[a])	92 (88.5[a])
Dexamethasone	111 (76.0[a])	91 (87.5[a])
Methylprednisolone	3 (2.1[a])	5 (4.8[a])
Prednisone	5 (3.4[a])	2 (1.9[a])
Further therapies		
Stem cells, NOS	7 (4.8[a])	4 (3.8[a])
Autologous stem cells, NOS	4 (2.7[a])	3 (2.9[a])

a. Institute's calculation based on the proportion of patients with subsequent therapy.

CAR: chimeric antigen receptor; DPd: daratumumab in combination with pomalidomide and dexamethasone; DVd: daratumumab in combination with bortezomib and dexamethasone; EPd: elotuzumab in combination with pomalidomide and dexamethasone; IRd: ixazomib in combination with lenalidomide and dexamethasone; Kd: carfilzomib in combination with dexamethasone; n: number of patients with subsequent therapy; N: number of analysed patients; NOS: not otherwise specified; RCT: randomized controlled trial

E.2 Results

Table 33: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (total population) (multipage table)

Study Outcome category Outcome	Idecabtagene vicleucel		Individualized therapy selected from DPd, DVd, IRd, Kd or EPd		Idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd
	N	Median time to event in months [95% CI][a] Patients with event n (%)	N	Median time to event in months [95% CI][a] Patients with event n (%)	HR [95% CI][b]; p-value[c]
KarMMa-3					
Mortality					
Overall survival	254	41.4 [31.0; NC] 106 (42)	132	38.0 [23.4; NC] 74 (56)	1.01 [0.73; 1.40]; 0.529[d]
Morbidity					
Symptoms (EORTC QLQ-C30, EORTC QLQ-MY20)			No suitable data[e]		
Health status (EQ-5D VAS)			No suitable data[e]		
Health-related quality of life					
EORTC QLQ-C30, EORTC QLQ-MY20			No suitable data[e]		
Side effects[f]					
Cytokine release syndrome			No suitable data[g]		
Severe neurological toxicity[h]	249	NA 19 (8)	126	NA 11 (9)	0.89 [0.42; 1.87]; 0.752
Infusion-related reactions			ND		
Severe infections[i]	249	NA 67 (27)	126	NA 36 (29)	0.97 [0.64; 1.45]; 0.863
Secondary malignancies[j]	249	NA 18 (7)	126	NA 10 (8)	0.99 [0.45; 2.16]; 0.972

Table 33: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (total population) (multipage table)

Study Outcome category Outcome	Idecabtagene vicleucel		Individualized therapy selected from DPd, DVd, IRd, Kd or EPd		Idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd
	N	Median time to event in months [95% CI][a] Patients with event n (%)	N	Median time to event in months [95% CI][a] Patients with event n (%)	HR [95% CI][b]; p-value[c]

a. Kaplan-Meier estimate.
b. HR and CI: Cox proportional hazards model, stratified by age, number of prior anti-myeloma therapies and high-risk cytogenetic abnormalities.
c. p-value: log-rank test, stratified by age, number of prior anti-myeloma therapies and high-risk cytogenetic abnormalities.
d. p-value: one-sided log-rank test, stratified by age, number of prior anti-myeloma therapies and high-risk cytogenetic abnormalities.
e. See Section 2.1.2 for reasons.
f. Based on analyses of any events occurring within the first 6 months after the infusion of idecabtagene vicleucel or the first dose in the control arm, as well as severe AEs (CTCAE grade ≥ 3), SAEs and AEs of special interest occurring in the period from Month 7 to 28 days after progression. In addition, severe AEs (CTCAE grade ≥ 3), SAEs and AEs of special interest that occurred during follow-up observation and were attributed to the study medication by the investigator, as well as any AEs that occurred in the control arm within 3 months of the treatment switch, were included in the analyses. No further specific AEs were selected on the basis of frequency.
g. See Section 2.2.2.1 for reasons.
h. Operationalized as nervous system disorders (SOC, severe AEs [CTCAE grade ≥ 3]).
i. Operationalized as infections and infestations (SOC, severe AEs [CTCAE grade ≥ 3]).
j. Operationalized as haematological malignant tumours (sub-SMQ [narrow]), non-haematological malignant tumours (sub-SMQ [narrow]), haematological tumours of unspecified malignancy (sub-SMQ [narrow]), non-haematological tumours of unspecified malignancy (sub-SMQ [narrow]) and myelodysplastic syndrome (ad hoc PT). The following PTs were excluded: plasma cell leukaemia, plasma cell myeloma in remission, plasma cell leukaemia in remission, plasma cell myeloma, plasma cell myeloma recurrent, plasma cell myeloma refractory, and plasmacytoma.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; DPd: daratumumab in combination with pomalidomide and dexamethasone; DVd: daratumumab in combination with bortezomib and dexamethasone; EORTC: European Organisation for Research and Treatment of Cancer; EPd: elotuzumab in combination with pomalidomide and dexamethasone; HR: hazard ratio; IRd: ixazomib in combination with lenalidomide and dexamethasone; Kd: carfilzomib in combination with dexamethasone; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

Table 34: Results (side effects, dichotomous) – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (total population)

Study Outcome category Outcome	Idecabtagene vicleucel		Individualized therapy selected from DPd, DVd, IRd, Kd or EPd		Idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
KarMMa-3					
Side effects[b]					
AEs (supplementary information)	249	248 (100)	126	125 (99)	
SAEs	249	104 (42)	126	50 (40)	1.05 [0.81; 1.37]; 0.736
Severe AEs[c]	249	230 (92)	126	105 (83)	1.11 [1.02; 1.21]; 0.007
Discontinuation due to AEs				ND	

a. Institute's calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [13]).
b. Based on analyses of events occurring up to 6 months after randomization.
c. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; DPd: daratumumab in combination with pomalidomide and dexamethasone; DVd: daratumumab in combination with bortezomib and dexamethasone; EPd: elotuzumab in combination with pomalidomide and dexamethasone; IRd: ixazomib in combination with lenalidomide and dexamethasone; Kd: carfilzomib in combination with dexamethasone; n: number of patients with (at least one) event; N: number of analysed patients; NC: not calculable; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

E.3 Kaplan-Meier curves

E.3.1 Mortality

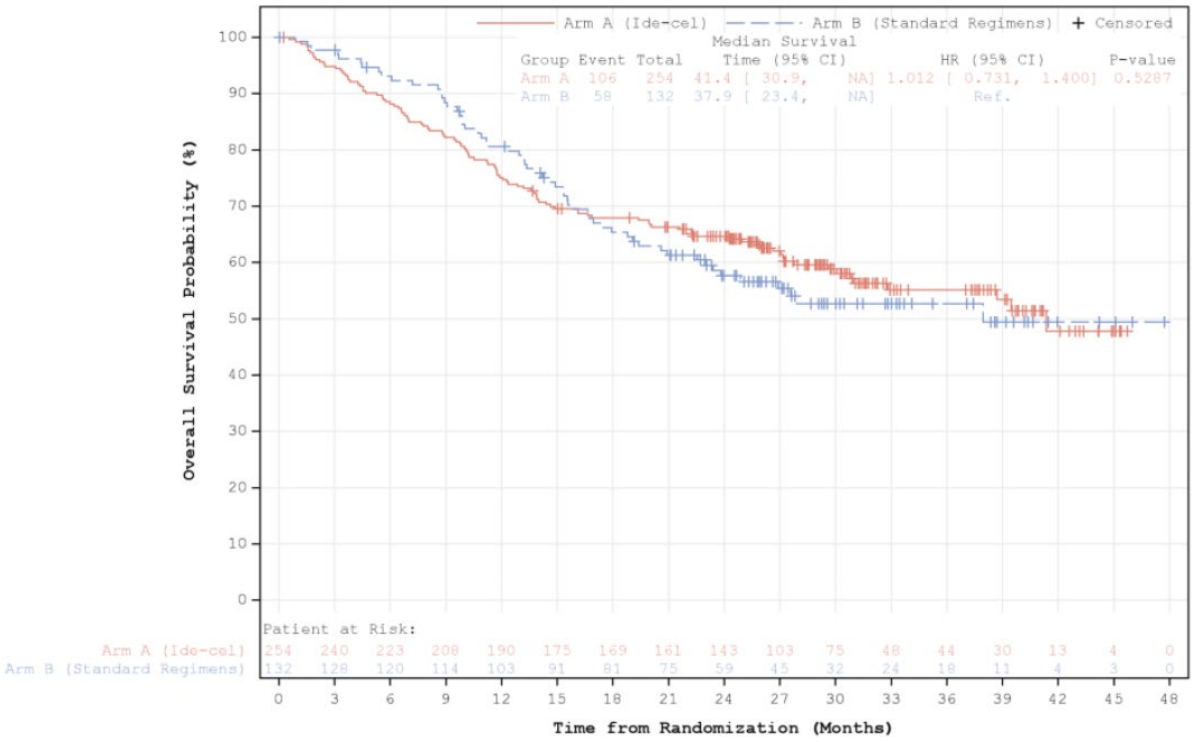

Figure 9: Kaplan-Meier curves for the outcome of overall survival, KarMMa-3 study, data cut-off: 28 April 2023, total population

E.3.2 Side effects

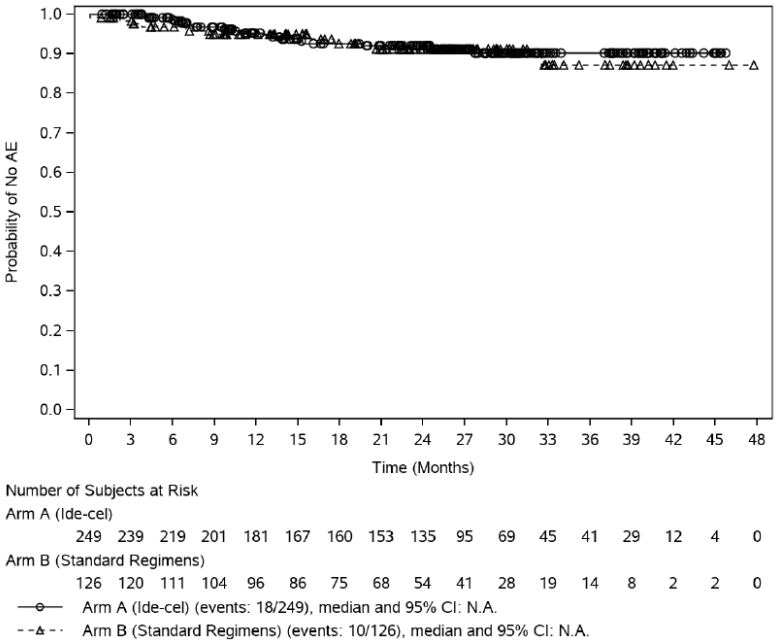

Figure 10: Kaplan-Meier curves for the outcome of secondary malignancies, KarMMa-3 study, data cut-off: 28 April 2023, total population

E.4 Results on side effects

For the overall rates of AEs, SAEs, and severe AEs (CTCAE grade ≥ 3), the following tables present events for MedDRA SOCs and PTs, each on the basis of the following criteria:

- overall rate of AEs (irrespective of severity): events which occurred in at least 10% of patients in one study arm
- overall rates of severe AEs (CTCAE grade ≥ 3) and SAEs: events which occurred in at least 5% of patients in one study arm
- additionally, for all events irrespective of severity: events which occurred in at least 10 patients and in at least 1% of patients in one study arm

For the outcome of discontinuation due to AEs, a complete presentation of all events (SOCs/PTs) that resulted in discontinuation is provided.

Table 35: Common AEs[a, b] – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (total population) (multipage table)

Study	**Patients with event n (%)**	
SOC[c] **PT[c]**	**Idecabtagene vicleucel** **N[d] = 249**	**Individualized therapy selected from DPd, DVd, IRd, Kd or EPd** **N[d] = 126**
KarMMa-3		
Overall AE rate	248 (99.6)	126 (100.0)
Blood and lymphatic system disorders	225 (90.4)	111 (88.1)
Neutropenia	196 (78.7)	91 (72.2)
Anaemia	165 (66.3)	75 (59.5)
Thrombocytopenia	138 (55.4)	68 (54.0)
Leukopenia	74 (29.7)	38 (30.2)
Lymphopenia	74 (29.7)	37 (29.4)
Febrile neutropenia	21 (8.4)	8 (6.3)
Immune system disorders	202 (81.1)	67 (53.2)
Cytokine release syndrome	197 (79.1)	65 (51.6)
Hypogammaglobulinaemia	22 (8.8)	11 (8.7)

Table 35: Common AEs[a, b] – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (total population) (multipage table)

Study	**Patients with event n (%)**	
SOC[c] **PT[c]**	**Idecabtagene vicleucel** **N[d] = 249**	**Individualized therapy selected from DPd, DVd, IRd, Kd or EPd** **N[d] = 126**
Gastrointestinal disorders	184 (73.9)	94 (74.6)
Nausea	113 (45.4)	66 (52.4)
Diarrhoea	86 (34.5)	51 (40.5)
Constipation	68 (27.3)	24 (19.0)
Vomiting	50 (20.1)	26 (20.6)
Abdominal pain	15 (6.0)	12 (9.5)
Gastrooesophageal reflux disease	12 (4.8)	4 (3.2)
Dyspepsia	11 (4.4)	5 (4.0)
General disorders and administration site conditions	169 (67.9)	99 (78.6)
Fatigue	70 (28.1)	54 (42.9)
Fever	68 (27.3)	39 (31.0)
Oedema peripheral	38 (15.3)	28 (22.2)
Asthenia	31 (12.4)	16 (12.7)
Chills	23 (9.2)	9 (7.1)
General physical health deterioration	19 (7.6)	6 (4.8)
Oedema	10 (4.0)	8 (6.3)
Metabolism and nutrition disorders	169 (67.9)	87 (69.0)
Hypokalaemia	80 (32.1)	39 (31.0)
Hypophosphataemia	79 (31.7)	28 (22.2)
Hypomagnesaemia	52 (20.9)	23 (18.3)
Decreased appetite	50 (20.1)	31 (24.6)
Hypocalcaemia	46 (18.5)	22 (17.5)
Hyponatraemia	25 (10.0)	11 (8.7)
Hypertriglyceridaemia	23 (9.2)	12 (9.5)
Hypercalcaemia	21 (8.4)	8 (6.3)
Hyperuricaemia	13 (5.2)	7 (5.6)
Hypoalbuminaemia	12 (4.8)	7 (5.6)
Hyperglycaemia	11 (4.4)	8 (6.3)
Dehydration	10 (4.0)	6 (4.8)

Table 35: Common AEs[a, b] – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (total population) (multipage table)

Study	**Patients with event n (%)**	
SOC[c] **PT[c]**	**Idecabtagene vicleucel** **N[d] = 249**	**Individualized therapy selected from DPd, DVd, IRd, Kd or EPd** **N[d] = 126**
Musculoskeletal and connective tissue disorders	157 (63.1)	81 (64.3)
Arthralgia	51 (20.5)	32 (25.4)
Back pain	48 (19.3)	26 (20.6)
Pain in extremity	33 (13.3)	26 (20.6)
Bone pain	23 (9.2)	12 (9.5)
Myalgia	18 (7.2)	10 (7.9)
Muscular weakness	17 (6.8)	15 (11.9)
Muscle spasms	12 (4.8)	18 (14.3)
Musculoskeletal chest pain	12 (4.8)	10 (7.9)
Neck pain	12 (4.8)	7 (5.6)
Pathological fracture	11 (4.4)	4 (3.2)
Infections and infestations	151 (60.6)	88 (69.8)
Upper respiratory tract infection	32 (12.9)	12 (9.5)
Pneumonia	28 (11.2)	12 (9.5)
COVID-19	16 (6.4)	17 (13.5)
Bladder inflammation	13 (5.2)	11 (8.7)
Bronchitis	12 (4.8)	4 (3.2)
Nervous system disorders	143 (57.4)	79 (62.7)
Headache	59 (23.7)	39 (31.0)
Neurotoxicity	34 (13.7)	15 (11.9)
Dizziness	28 (11.2)	17 (13.5)
Peripheral sensory neuropathy	13 (5.2)	21 (16.7)
Tremor	5 (2.0)	10 (7.9)

Table 35: Common AEs[a, b] – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (total population) (multipage table)

Study	**Patients with event n (%)**	
SOC[c] **PT[c]**	**Idecabtagene vicleucel** **N[d] = 249**	**Individualized therapy selected from DPd, DVd, IRd, Kd or EPd** **N[d] = 126**
Respiratory, thoracic and mediastinal disorders	121 (48.6)	77 (61.1)
Dyspnoea	44 (17.7)	36 (28.6)
Cough	39 (15.7)	26 (20.6)
Nasal congestion	16 (6.4)	9 (7.1)
Oropharyngeal pain	16 (6.4)	6 (4.8)
Hypoxia	13 (5.2)	5 (4.0)
Epistaxis	12 (4.8)	7 (5.6)
Pleural effusion	12 (4.8)	7 (5.6)
Rhinorrhoea	11 (4.4)	6 (4.8)
Productive cough	10 (4.0)	5 (4.0)
Investigations	102 (41.0)	61 (48.4)
Alanine aminotransferase increased	22 (8.8)	12 (9.5)
Aspartate aminotransferase increased	22 (8.8)	15 (11.9)
Gamma-glutamyltransferase increased	22 (8.8)	6 (4.8)
Weight decreased	19 (7.6)	12 (9.5)
Blood alkaline phosphatase increased	17 (6.8)	6 (4.8)
C-reactive protein increased	16 (6.4)	6 (4.8)
Blood creatinine increased	15 (6.0)	12 (9.5)
Weight increased	13 (5.2)	10 (7.9)
Fibrin D dimer increased	11 (4.4)	3 (2.4)
Vascular disorders	91 (36.5)	43 (34.1)
Hypertension	41 (16.5)	28 (22.2)
Hypotension	37 (14.9)	16 (12.7)
Skin and subcutaneous tissue disorders	74 (29.7)	46 (36.5)
Rash	19 (7.6)	10 (7.9)
Pruritus	14 (5.6)	14 (11.1)
Alopecia	13 (5.2)	6 (4.8)
Cardiac disorders	66 (26.5)	34 (27.0)
Tachycardia	25 (10.0)	9 (7.1)
Sinus tachycardia	14 (5.6)	9 (7.1)
Sinus bradycardia	10 (4.0)	2 (1.6)

Table 35: Common AEs[a, b] – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (total population) (multipage table)

Study	**Patients with event n (%)**	
SOC[c] **PT[c]**	**Idecabtagene vicleucel** **N[d] = 249**	**Individualized therapy selected from DPd, DVd, IRd, Kd or EPd** **N[d] = 126**
Psychiatric disorders	61 (24.5)	47 (37.3)
Insomnia	40 (16.1)	28 (22.2)
Anxiety	16 (6.4)	9 (7.1)
Injury, poisoning and procedural complications	55 (22.1)	41 (32.5)
Fall	16 (6.4)	9 (7.1)
Contusion	10 (4.0)	10 (7.9)
Renal and urinary disorders	54 (21.7)	24 (19.0)
Acute kidney injury	16 (6.4)	8 (6.3)
Renal failure	10 (4.0)	5 (4.0)
Eye disorders	30 (12.0)	25 (19.8)
Vision blurred	8 (3.2)	12 (9.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	21 (8.4)	10 (7.9)
Hepatobiliary disorders	18 (7.2)	8 (6.3)
Ear and labyrinth disorders	13 (5.2)	4 (3.2)
Reproductive system and breast disorders	11 (4.4)	3 (2.4)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. Based on analyses of any events occurring within the first 6 months after the infusion of idecabtagene vicleucel or the first dose in the control arm, as well as severe AEs (CTCAE grade ≥ 3), SAEs and AEs of special interest occurring in the period from Month 7 to 28 days after progression. In addition, severe AEs (CTCAE grade ≥ 3), SAEs and AEs of special interest that occurred during follow-up observation and were attributed to the study medication by the investigator, as well as any AEs that occurred in the control arm within 3 months of the treatment switch, were included in the analyses.
c. MedDRA version 24.1 or higher; SOCs and PTs taken from Module 4 without adaptation.
d. Treated patients; in the comparator arm, patients continued to be analysed in the comparator arm in accordance with their randomization even after switching treatment.

AE: adverse event; COVID-19: coronavirus disease 2019; CTCAE: Common Terminology Criteria for Adverse Events; DPd: daratumumab in combination with pomalidomide and dexamethasone; DVd: daratumumab in combination with bortezomib and dexamethasone; EPd: elotuzumab in combination with pomalidomide and dexamethasone; IRd: ixazomib in combination with lenalidomide and dexamethasone; Kd: carfilzomib in combination with dexamethasone; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 36: Common SAEs[a, b] – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (total population)

Study	**Patients with event n (%)**	
SOC[c] **PT[c]**	**Idecabtagene vicleucel N[d] = 249**	**Individualized therapy selected from DPd, DVd, IRd, Kd or EPd N[d] = 126**
KarMMa-3		
Overall SAE rate	139 (55.8)	78 (61.9)
Infections and infestations	67 (26.9)	36 (28.6)
Pneumonia	17 (6.8)	8 (6.3)
General disorders and administration site conditions	34 (13.7)	15 (11.9)
General physical health deterioration	17 (6.8)	6 (4.8)
Fever	12 (4.8)	2 (1.6)
Blood and lymphatic system disorders	20 (8.0)	11 (8.7)
Febrile neutropenia	10 (4.0)	5 (4.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	19 (7.6)	8 (6.3)
Nervous system disorders	19 (7.6)	11 (8.7)
Neurotoxicity	10 (4.0)	3 (2.4)
Musculoskeletal and connective tissue disorders	17 (6.8)	14 (11.1)
Renal and urinary disorders	13 (5.2)	5 (4.0)
Respiratory, thoracic and mediastinal disorders	13 (5.2)	14 (11.1)
Cardiac disorders	12 (4.8)	10 (7.9)
Immune system disorders	12 (4.8)	0 (0)
Cytokine release syndrome	10 (4.0)	0 (0)
Metabolism and nutrition disorders	11 (4.4)	4 (3.2)

a. Events that occurred in ≥ 10 patients in the intervention arm, or in ≥ 5% of patients in the comparator arm.
b. Based on analyses of any events occurring within the first 6 months after the infusion of idecabtagene vicleucel or the first dose in the control arm, as well as severe AEs (CTCAE grade ≥ 3), SAEs and AEs of special interest occurring in the period from Month 7 to 28 days after progression. In addition, severe AEs (CTCAE grade ≥ 3), SAEs and AEs of special interest that occurred during follow-up observation and were attributed to the study medication by the investigator, as well as any AEs that occurred in the control arm within 3 months of the treatment switch, were included in the analyses.
c. MedDRA version 24.1 or higher; SOCs and PTs taken from Module 4 without adaptation.
d. Treated patients; in the comparator arm, patients continued to be analysed in the comparator arm in accordance with their randomization even after switching treatment.

CTCAE: Common Terminology Criteria for Adverse Events; DPd: daratumumab in combination with pomalidomide and dexamethasone; DVd: daratumumab in combination with bortezomib and dexamethasone; EPd: elotuzumab in combination with pomalidomide and dexamethasone; IRd: ixazomib in combination with lenalidomide and dexamethasone; Kd: carfilzomib in combination with dexamethasone; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 37: Common severe AEs (CTCAE grade ≥ 3)[a, b] – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (total population) (multipage table)

Study	**Patients with event n (%)**	
SOC[c] **PT[c]**	**Idecabtagene vicleucel N[d] = 249**	**Individualized therapy selected from DPd, DVd, IRd, Kd or EPd N[d] = 126**
KarMMa-3		
Overall rate of severe AEs (CTCAE grade ≥ 3)	236 (94.8)	120 (95.2)
Blood and lymphatic system disorders	219 (88.0)	109 (86.5)
Neutropenia	190 (76.3)	91 (72.2)
Anaemia	127 (51.0)	59 (46.8)
Thrombocytopenia	108 (43.4)	53 (42.1)
Leukopenia	73 (29.3)	36 (28.6)
Lymphopenia	71 (28.5)	36 (28.6)
Febrile neutropenia	21 (8.4)	7 (5.6)
Metabolism and nutrition disorders	90 (36.1)	35 (27.8)
Hypophosphataemia	50 (20.1)	12 (9.5)
Hypocalcaemia	13 (5.2)	4 (3.2)
Hypokalaemia	11 (4.4)	4 (3.2)
Hyponatraemia	11 (4.4)	3 (2.4)
Hypercalcaemia	10 (4.0)	3 (2.4)
Infections and infestations	66 (26.5)	36 (28.6)
Pneumonia	19 (7.6)	8 (6.3)
General disorders and administration site conditions	33 (13.3)	21 (16.7)
General physical health deterioration	17 (6.8)	6 (4.8)
Investigations	30 (12.0)	19 (15.1)
Gamma-glutamyltransferase increased	11 (4.4)	4 (3.2)
Vascular disorders	29 (11.6)	17 (13.5)
Hypertension	23 (9.2)	16 (12.7)
Respiratory, thoracic and mediastinal disorders	23 (9.2)	12 (9.5)
Nervous system disorders	21 (8.4)	15 (11.9)
Musculoskeletal and connective tissue disorders	20 (8.0)	20 (15.9)
Renal and urinary disorders	17 (6.8)	8 (6.3)
Immune system disorders	15 (6.0)	2 (1.6)
Cytokine release syndrome	11 (4.4)	0 (0)
Cardiac disorders	14 (5.6)	12 (9.5)
Gastrointestinal disorders	13 (5.2)	6 (4.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10 (4.0)	4 (3.2)

Table 37: Common severe AEs (CTCAE grade ≥ 3)[a, b] – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (total population) (multipage table)

Study	Patients with event n (%)	
SOC[c] PT[c]	Idecabtagene vicleucel N[d] = 249	Individualized therapy selected from DPd, DVd, IRd, Kd or EPd N[d] = 126

a. Events that occurred in ≥ 10 patients in the intervention arm, or in ≥ 5% of patients in the comparator arm.
b. Based on analyses of any events occurring within the first 6 months after the infusion of idecabtagene vicleucel or the first dose in the control arm, as well as severe AEs (CTCAE grade ≥ 3), SAEs and AEs of special interest occurring in the period from Month 7 to 28 days after progression. In addition, severe AEs (CTCAE grade ≥ 3), SAEs and AEs of special interest that occurred during follow-up observation and were attributed to the study medication by the investigator, as well as any AEs that occurred in the control arm within 3 months of the treatment switch, were included in the analyses.
c. MedDRA version 24.1 or higher; SOCs and PTs taken from Module 4 without adaptation.
d. Treated patients; in the comparator arm, patients continued to be analysed in the comparator arm in accordance with their randomization even after switching treatment.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; DPd: daratumumab in combination with pomalidomide and dexamethasone; DVd: daratumumab in combination with bortezomib and dexamethasone; EPd: elotuzumab in combination with pomalidomide and dexamethasone; IRd: ixazomib in combination with lenalidomide and dexamethasone; Kd: carfilzomib in combination with dexamethasone; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 38: Discontinuations due to AEs – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (total population)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Idecabtagene vicleucel N[b] = 249**	**Individualized therapy selected from DPd, DVd, IRd, Kd or EPd N[b] = 126**
KarMMa-3		
Overall rate of discontinuations due to AEs	3 (1.2)	8 (6.3)
Blood and lymphatic system disorders	1 (0.4)	3 (2.4)
Leukopenia	0 (0)	2 (1.6)
Thrombocytopenia	1 (0.4)	1 (0.8)
Neutropenia	0 (0)	1 (0.8)
Cardiac disorders	0 (0)	1 (0.8)
Cardiac failure congestive	0 (0)	1 (0.8)
Gastrointestinal disorders	0 (0)	1 (0.8)
Diarrhoea	0 (0)	1 (0.8)
General disorders and administration site conditions	0 (0)	1 (0.8)
Chills	0 (0)	1 (0.8)
Hepatobiliary disorders	1 (0.4)	0 (0)
Hypertransaminasaemia	1 (0.4)	0 (0)
Infections and infestations	1 (0.4)	0 (0)
Influenza	1 (0.4)	0 (0)
Metabolism and nutrition disorders	0 (0)	1 (0.8)
Hypercalcaemia	0 (0)	1 (0.8)
Respiratory, thoracic and mediastinal disorders	1 (0.4)	1 (0.8)
Dyspnoea	1 (0.4)	0 (0)
Pulmonary embolism	0 (0)	1 (0.8)
Skin and subcutaneous tissue disorders	1 (0.4)	0 (0)
Urticaria	1 (0.4)	0 (0)

a. MedDRA version 24.1 or higher; SOCs and PTs taken from Module 4 without adaptation.
b. Treated patients; in the comparator arm, patients continued to be analysed in the comparator arm in accordance with their randomization even after switching treatment.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

E.5 Results on side effects (censoring at 6 months or at progression, whichever occurred later)

Table 39: Results (side effects, time to event) – RCT, direct comparison: idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd (total population)

Study Outcome category Outcome	Idecabtagene vicleucel		Individualized therapy selected from DPd, DVd, IRd, Kd or EPd		Idecabtagene vicleucel vs. individualized therapy selected from DPd, DVd, IRd, Kd or EPd
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][a]; p-value[b]
KarMMa-3					
Side effects[c]					
AEs	249	0.3 [0.3; 0.4] 248 (100)	126	0.3 [0.3; 0.3] 126 (100)	–
SAEs	249	7.8 [6.3; 13.4] 138 (55)	126	7.3 [0.7; 1.3] 78 (62)	0.97 [0.73; 1.28]; 0.797
Severe AEs[d]	249	1.5 [1.3; 1.6] 235 (94)	126	1.4 [1.0; 1.8] 120 (95)	1.47 [1.16; 1.86]; 0.001
Discontinuation due to AEs				ND	

a. Stratified Cox proportional hazards model.
b. p-value: log-rank test, stratified by age, number of prior anti-myeloma therapies and high-risk cytogenetic abnormalities.
c. Based on analyses with censoring 6 months after randomization or 28 days after progression/end of treatment, whichever occurs later.
d. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; DPd: daratumumab in combination with pomalidomide and dexamethasone; DVd: daratumumab in combination with bortezomib and dexamethasone; EPd: elotuzumab in combination with pomalidomide and dexamethasone; HR: hazard ratio; IRd: ixazomib in combination with lenalidomide and dexamethasone; Kd: carfilzomib in combination with dexamethasone; n: number of patients with (at least one) event; N: number of analysed patients; NC: not calculable; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event

E.6 Kaplan-Meier curves for the supplementary presentation of results on side effects (censoring at 6 months or at progression, whichever occurred later)

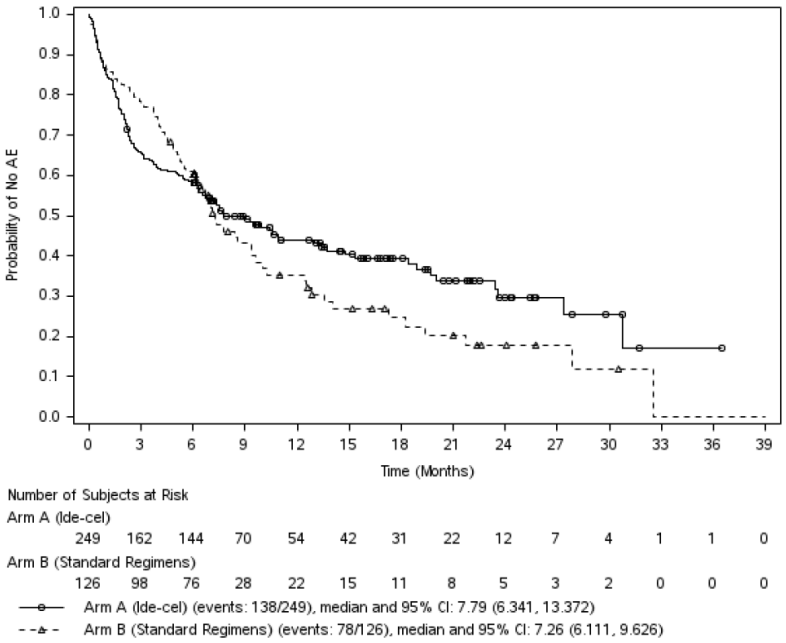

Figure 11: Kaplan-Meier curves for the outcome of SAEs, KarMMa-3 study, data cut-off: 28 April 2023, total population

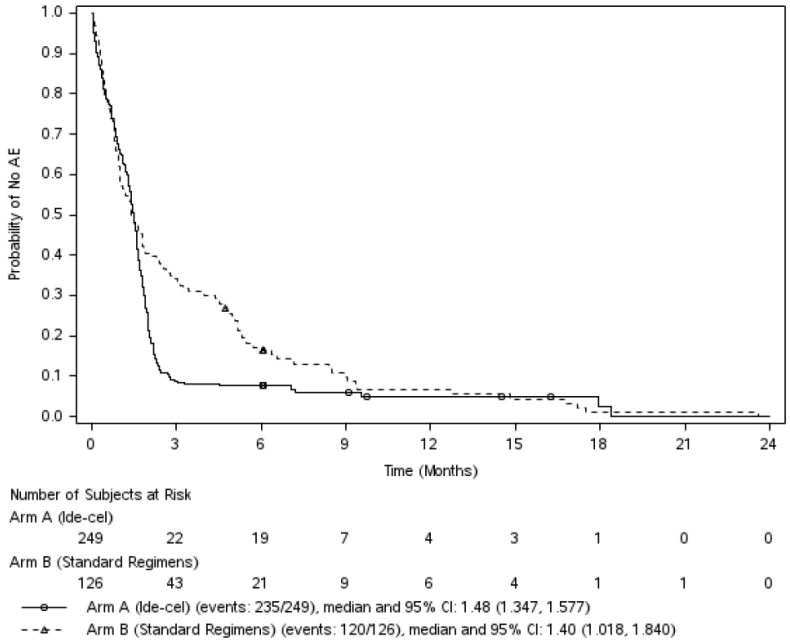

Figure 12: Kaplan-Meier curves for the outcome of severe AEs (CTCAE grade ≥ 3), KarMMa-3 study, data cut-off: 28 April 2023, total population