Ciltacabtagene autoleucel (multiple myeloma)

Addendum to Project A24-116 (dossier assessment)[1]

ADDENDUM (DOSSIER ASSESSMENT)

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CAR	chimeric antigen receptor
CTCAE	Common Terminology Criteria for Adverse Events
DPd	daratumumab in combination with pomalidomide and dexamethasone
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMRM	mixed-effects model repeated measures
MySIm-Q	Multiple Myeloma Symptom and Impact Questionnaire
PGIS	Patient Global Impression of Severity
PT	Preferred Term
PVd	pomalidomide in combination with bortezomib and dexamethasone
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
VAS	visual analogue scale

1 Background

On 8 April 2025, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A24-116 (Ciltacabtagene autoleucel – Benefit assessment according to § 35a Social Code Book V) [1].

The commission comprises the assessment of the following analyses of the CARTITUDE-4 study [2,3] presented by the pharmaceutical company (hereinafter referred to as the "company") in the commenting procedure:

- side effects: missing information and supplementary sensitivity analyses
- patient-reported outcomes: information and supplementary sensitivity analyses
  - morbidity: health status (recorded using the EQ-5D visual analogue scale [VAS]) and symptoms (recorded using the European Organisation for Research and Treatment Quality of Life Questionnaire - Core 30 [EORTC QLQ-C30], Patient Global Impression of Severity [PGIS], Multiple Myeloma Symptom and Impact Questionnaire [MySIm-Q] Total Symptom Score)
  - health-related quality of life: assessed using the EORTC QLQ-C30 and MySIm-Q Total Impact Score

The commission also includes an assessment/discussion of which of the submitted sensitivity analyses is best suited for the benefit assessment. In addition, the presentation of sensitivity analysis 1 (time to first deterioration) and sensitivity analysis 2 (continuous analysis using an mixed-effects model repeated measures [MMRM]) is included in the commission for the patient-reported outcomes mentioned above.

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

The randomized controlled trial (RCT) CARTITUDE-4 was included for the benefit assessment of ciltacabtagene autoleucel compared with an individualized treatment as appropriate comparator therapy (ACT) in adult patients with relapsed and refractory multiple myeloma who have previously received at least 1 therapy, including 1 immunomodulator and 1 proteasome inhibitor, and who have demonstrated disease progression during the last therapy and are refractory to lenalidomide. A detailed description of the study can be found in dossier assessment A24-116 [1].

As described in dossier assessment A24-116, no suitable data were available for the benefit assessment for outcomes in the categories of morbidity and health-related quality of life and the majority of outcomes in the side effects category (except severe adverse events [AEs] and discontinuation due to AEs).

The data recorded in the study are not meaningfully interpretable for the patient-reported outcomes, because relevant periods of the chimeric antigen receptor (CAR) T cell therapy were not taken into account in the recordings and a fair comparison of the treatment concepts in the two treatment arms in the sense of the research question is therefore impossible. In addition, there were further uncertainties or ambiguities for individual patient-reported outcomes (for the MySIm-Q with regard to validation, for the health status [assessed using EQ-5D VAS] with regard to the failure to record data until the end of the study [see Section I.4.1 of dossier assessment A24-116]).

In the side effects category, the analyses presented by the company in the dossier are not suitable for the majority of outcomes, as certain events per patient were selectively recorded during follow-up and these phases were taken into account in the analyses. As part of the commenting procedure, the company subsequently submitted information and supplementary sensitivity analyses for both outcomes in the side effects category and for patient-reported outcomes in the categories of morbidity and health-related quality of life. In accordance with the commission, information and sensitivity analysis subsequently submitted by the company in the commenting procedure are assessed below.

2.1 Results

2.1.1 Information and sensitivity analyses on patient-reported outcomes

As described in dossier assessment A24-116, the data for the patient-reported outcomes are not meaningfully interpretable irrespective of the analysis, because relevant periods of the CAR T cell therapy were not taken into account in the recordings and a fair comparison of the treatment concepts in the two treatment arms in the sense of the research question is therefore impossible (see Figure 1).

The relevant treatment phases in which no recordings were conducted in the intervention arm are:

- the median duration of the treatment phase in which the bridging therapy was administered; approx. 2.6 months
- the period between lymphodepleting chemotherapy and 28 days after CAR T cell infusion (no recordings took place on the day of CAR T cell infusion); a total of approx. 5 weeks

However, these treatment phases are part of the treatment concept in the intervention arm and must therefore be taken into account in the recording of patient-reported outcomes. In the control arm, in contrast, patient-reported outcomes are recorded continuously and more frequently immediately from the start of treatment after randomization.

It should also be noted that the duration of the periods without recording the patient-reported outcomes varied individually for the patients in the intervention arm of the CARTITUDE-4 study. This applies in particular to the period of bridging therapy. Although no specific data are available for this period, the median duration from leukapheresis to CAR T cell infusion in the study was 2.6 months (min/max 1.5 to 8.1 months). Since the time periods between leukapheresis and the start of bridging therapy or between lymphodepleting chemotherapy and infusion of ciltacabtagene autoleucel are negligible according to the study design, it can be derived that the possible time periods under bridging therapy differ only slightly from these figures. In addition, according to the study design, there were about 5 weeks between lymphodepleting chemotherapy and the next follow-up recording after CAR T cell infusion, during which no patient-reported outcomes were recorded in the intervention arm. This means that the recording of patient-reported outcomes was omitted over months in the intervention arm and therefore no conclusion can be drawn in the sense of the research question about symptoms and health-related quality of life in relevant treatment phases.

2.1.1.1 Sensitivity analyses of patient-reported outcomes subsequently submitted by the company

In its comments, the company presented various sensitivity analyses which, in its view, confirm that there is no potential disadvantage for the control arm due to the data recording times chosen in the study. In doing so, it presents analyses on the time to first or first confirmed deterioration in which, in contrast to the analyses presented in the dossier, selected recording time points in the first 1 to 2 months of the study are not taken into account (sensitivity analysis 1). For details on the recording time points excluded from these analyses, see Figure 1. In addition, it presents analyses using mean differences from MMRM analyses, which include all time points of recording of the CARTITUDE-4 study (sensitivity analysis 2).

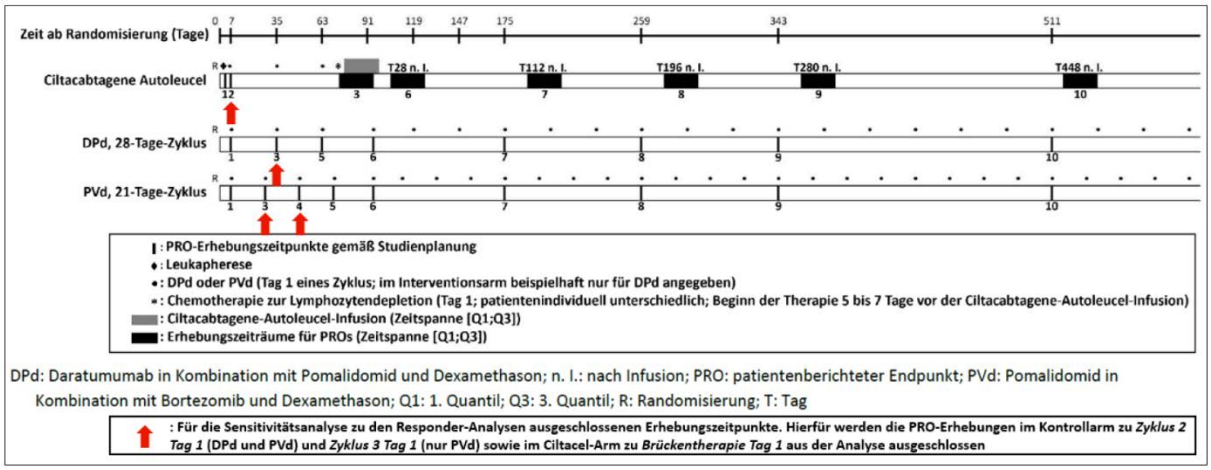

Figure 1: Overview of the planned recording time points of the CARTITUDE 4 study considered in sensitivity analysis 1 on patient-reported outcomes (taken from the company's comments)

Zeit ab Randomisierung	Time from randomization
Tage	Days
28-Tage-Zyklus	28-day cycle
PRO-Erhebungszeitpunkte gemäß Studienplanung	PRO survey dates according to the study design
Leukapherese	Leukapheresis
DPd oder PVD (Tag 1 eines Zyklus; im Interventionsarm beispielhaft nur für DPd angegeben)	DPd or PVD (Day 1 of a cycle; in the intervention arm only indicated for DPd as an example)
Chemotherapie zur Lymhozytendepletion (Tag 1: patientenindividuell unterschiedlich; Beginn der Therapie 5 bis 7 Tage vor der Ciltacabtagen-Autoleucel-Infusion)	Lymphodepleting chemotherapy (Day 1: varies from patient to patient; start of therapy 5 to 7 days before ciltacabtagene autoleucel infusion)
Ciltacabtagen-Autoleucel-Infusion (Zeitspanne [Q1; Q3])	Ciltacabtagene-autoleucel infusion (period [Q1; Q3])
Erhebungszeiträume für PROs (Zeitspanne [Q1; Q3])	Survey periods for PROs (period [Q1; Q3])
DPd: Daratumumab in Kombination mit Pomalidomid und Dexamethason; n.I.: nach Infusion; PRO: patienentberichteter Endpunkt; PVd: Pomalidomid in Kombination mit Bortezomib und Dexamethason; Q1: erstes Quantil; Q3: drittes Quantil; R: Randomisierung; T: Tag	DPd: Daratumumab in combination with pomalidomide and dexamethasone; n.I.: following infusion; PRO: patient-reported outcome; PVd: pomalidomide in combination with bortezomib and dexamethasone; Q1: first quantile; Q3: third quantile; R: randomization; D: Day
Für die Sensitivitätsanalyse zu den Responderanalysen ausgeschlossenen Erhebungszeitpunkte. Hierfür werden die PRO-Erhebungen im Kontrollarm zu Zyklus 2 Tag 1 (DPd und PVd) und Zyklus 3 Tag 1 (nur PVd) sowie im Ciltacel-Arm zur Brückentherapie Tag 1 aus der Analyse ausgeschlossen	Survey time points excluded for the sensitivity analysis on the responder analyses. For this purpose, the PRO surveys in the control arm on Cycle 2 Day 1 (DPd and PVd) and Cycle 3 Day 1 (PVd only) as well as (in the ciltacel arm) on the bridging therapy Day 1 are excluded from the analysis.

Responder analyses subsequently presented by the company on the time to first or first confirmed deterioration (sensitivity analysis 1) not suitable for the benefit assessment

In its comments, the company presented responder analyses for the patient-reported outcomes for the time to the first or first confirmed deterioration, in which individual recordings in the intervention and control arm are not considered. These analyses do not consider recording time point 2 at the start of the 1st cycle of the bridging therapy in the intervention arm, nor does it consider recording time points 3 and possibly 4 at the start of the 2nd cycle or 3rd cycle of the comparator therapy in the control arm (sensitivity analysis 1; see Figure 1). The sensitivity analysis 1 subsequently submitted by the company is not suitable for answering the research question of the benefit assessment. Although the company's approach of not considering all recording time points in the analyses means that the same number of recording time points are included in both study arms, it is still not possible to draw a conclusion about the symptoms and health-related quality of life in relevant treatment phases. This is due to the fact that relevant treatment phases in this sensitivity analysis are now not considered in the analyses in both treatment arms. This does not allow a comparison of the two treatment concepts in the sense of the research question. The extent to which the results are influenced in favour of ciltacabtagene autoleucel by the lack of recordings in the intervention arm cannot be assessed due to the non-consideration of recording time points on the comparator side in sensitivity analyses.

Irrespective of the fundamental unsuitability of sensitivity analysis 1, there is another reason why the analyses on the time to first confirmed deterioration cannot be meaningfully interpreted in the present data situation. In the CARTITUDE-4 study, the observation period for the patient-reported outcomes was linked to the treatment duration and thus systematically shortened compared with overall survival, and moreover, it clearly differed between the treatment arms (see Table 11 in dossier assessment A24-116 [1]). Median observation in the intervention arm was more than twice as long as in the comparator arm (around 24 months versus 9 months). In this data situation, recording of a first confirmed deterioration is potentially less probable in the comparator arm than in the intervention arm due to the shorter observation period; a meaningful interpretation of the results is therefore impossible. A supplementary presentation of the sensitivity analysis 1 (time to first confirmed deterioration) presented by the company is therefore not provided in this addendum.

Continuous analysis by means of MMRM (sensitivity analysis 2) subsequently submitted by the company not suitable for the benefit assessment

In the dossier, analyses on the change from baseline using MMRM are available for selected patient-reported outcomes on morbidity and health-related quality of life. As described in the dossier assessment, these analyses only take into account recording time points in the two study arms that can be assigned to each other in terms of time (recording time points 1, 2 and 6 for the intervention arm, recording time points 1 and 6 for the control arm; see Figure 1).

The proportion of patients included in these analyses differs significantly between the study arms. In addition to the described deficiencies in the recording, the continuous analyses were therefore not suitable for the benefit assessment due to highly differentiated responses.

With sensitivity analysis 2, the company presents analyses per mean difference using MMRM in its comments, which, according to the company, considers all prespecified recording time points. In contrast to the analyses available in the dossier's study documents, the differences in the patients considered are therefore not strongly differentiated between the study arms for sensitivity analysis 2. Nevertheless, these analyses are also not suitable for the benefit assessment. This is due to the fact that in the control arm, recordings under bridging therapy were taken into account for which there is no recording time counterpart from the intervention arm (recording time points 3, possibly 4 and 5, see Figure 1). As a result, in sensitivity analysis 2, relevant treatment phases in the comparator arm were included in the analyses, while these were not recorded in the intervention arm. It is not possible to estimate how this affects the results of the MMRM analyses.

In addition, there are methodological uncertainties for sensitivity analysis 2. Firstly, the exact implementation in the MMRM remains unclear. The company states that no time-interaction term was used in the statistical model. In principle, a model without an interaction term between time and treatment arm makes a calculation feasible, even if no values are available for all patients in one of the arms at one or more points in time. However, it remains unclear which recording time points in the control arm remain without a time counterpart from the intervention arm or which recording time points among the various therapies in the control arm may be summarized for the analysis and which recording time points in the intervention arm these are compared with. Moreover, although the treatment effect is estimated over the entire observation period - and not only at a single recording time point - without the mentioned interaction term, as described by the company, possible differences between the treatment arms with regard to the density of recordings in certain study phases only have no potentially biasing influence on the analysis results if the incoming data are also representative of the course in the study phases not covered. However, this cannot be assumed in the present data situation, as the phase under bridging therapy and the phase immediately after the CAR T cell infusion do not include therapy phases in the intervention arm in which patients are potentially exposed to greater treatment-related burdens.

It should also be noted that due to the shortened median observation period for the patient-reported outcomes of around 9 months in the comparator arm and around 24 months in the intervention arm, it is not possible to draw any conclusions about the comparison of the treatment concepts over the entire study period up to the data cut-off on the basis of continuous analyses.

Summarized assessment of sensitivity analyses 1 and 2

Due to the design-related lack of data recordings on patient-reported outcomes during relevant treatment phases in the intervention arm, the results on the patient-reported outcomes cannot be used to answer the research question of the benefit assessment. This deficiency cannot be remedied by adapted analyses. Consequently, none of the sensitivity analyses presented by the company is suitable for the benefit assessment.

In accordance with the present commission, the sensitivity analyses 1 and 2 are presented in Appendix D.1 and Appendix D.2 as supplementary information.

2.1.1.2 Information on MySIm-Q subsequently presented by the company

For the patient-reported MySIm-Q developed by the company, the dossier particularly lacked information on investigations of the psychometric properties of the total impact score, so that it remained unclear whether the validation of the MySIm-Q had already been completed. In its comments, the company subsequently submitted information on the validation, which included further analyses of the instrument, including the total impact score. From the subsequently submitted data together with the sources on the development of the MySIm-Q presented by the company in the dossier, it can be derived that this can be used as a valid instrument for the recording of symptoms and impairments in patients with multiple myeloma.

2.1.2 Information and sensitivity analyses on outcomes of the side effects category

In the CARTITUDE-4 study, AEs, the severe AEs based on them (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3), serious AEs (SAEs) and AEs of special interest to patients were recorded in full for different lengths of time between the two treatment arms. Based on the dossier, there were uncertainties regarding the time period over which all events were completely recorded and which time periods were considered in the analyses presented by the company in the dossier. Moreover, in both treatment arms, the analyses also considered AEs, SAEs and severe AEs recorded after the end of the complete survey if the investigator suspected a causal relationship with the study medication. With the exception of the analyses on the overall rates of the outcomes of discontinuation due to AEs and severe AEs (CTCAE grade ≥ 3), the analyses on outcomes in the side effects category presented by the company in the dossier were therefore not suitable for the benefit assessment (for a detailed explanation, see Section I 4.1 of dossier assessment A24-116 [1]).

With the comments, the company subsequently submitted information and sensitivity analyses on the outcomes in the side effects category, which largely clarify the uncertainties described in dossier assessment A24-116. This is explained below.

2.1.2.1 Information subsequently submitted by the company on the recording of AEs in the CARTITUDE-4 study

The company provides information on the time point in the study up to which, depending on the assigned therapy and the course of treatment, a complete observation of all events for the individual patient took place. Figure 2 shows a summary of these data for the observation of AEs, the severe AEs based on them (CTCAE grade ≥ 3), SAEs and AEs of special interest.

Studienarm	Patientenpopulation	Jegliche UE & Schwere UE ≥ Grad 3	Schwerwiegende UE	UE von besonderem Interesse - Sekundär-malignome	UE von besonderem Interesse – CRS und Neurotoxizität, Delayed UE
Ciltacel-Arm	Patienten ohne Progress während der Überbrückungstherapie, die Ciltacel als Studienmedikation erhalten haben	Bis Tag 112 nach Ciltacel-Infusion[a]	Bis zum Studienende	Bis zum Studienende	Bis zum Studienende
	Patienten mit Progress während oder nach der Überbrückungstherapie, die Ciltacel in der nächsten Therapielinie als Folgetherapie erhalten haben	Bis Tag 112 nach Ciltacel-Infusion[a]	Bis zum Studienende	Bis zum Studienende	Bis zum Studienende
	Patienten mit Progress während oder nach der Überbrückungstherapie die kein Ciltacel erhalten haben	Bis 30 Tage nach der letzten Dosis der Überbrückungstherapie	Bis 30 Tage nach der letzten Dosis der Überbrückungstherapie	Bis zum Studienende	–[b]
Kontrollarm		Bis 30 Tage nach der letzten Dosis der Studienmedikation oder zum Beginn der Folgetherapie, je nachdem, was zuerst eintritt[a]	Bis 30 Tage nach der letzten Dosis der Studienmedikation oder zum Beginn der Folgetherapie, je nachdem, was zuerst eintritt[a]	Bis zum Studienende	–[b]

a: Nach diesen Zeitpunkten werden zusätzlich bis zum Studienende alle UE, die laut Einschätzung des Prüfarztes im Kausalzusammenhang mit der jeweiligen Studienmedikation stehen, erhoben.
b: Sofern ein CRS oder ein eine Neurotoxizität charakterisierendes UE im Rahmen der Auswertungen für Jegliche UE, Schwere UE ≥ Grad 3 oder Schwerwiegende UE in den jeweiligen Auswertungszeiträumen im Kontrollarm auftritt, wird dies in der Auswertung auf SOC/PT Ebene ersichtlich. Eine präspezifizierte Auswertung als UE von besonderem Interesse ist im Kontrollarm jedoch nicht vorgesehen.

AE: adverse event; ciltacel: ciltacabtagene autoleucel; CRS: cytokine release syndrome; PT: Preferred Term; SOC: System Organ Class

Figure 2: Recording of AEs within the framework of the CARTITUDE-4 study (taken from the company's comments)

Study arm	Patient population	Any AE and severe AE ≥ grade 3	Serious AEs	AEs of special interest – secondary malignancies	AEs of special interest – CRS and neurotoxicity, delayed AEs
Ciltacel arm	Patients without progress under the bridging therapy who received ciltacel as study medication	Until Day 112 after ciltacel infusion[a]	Until the end of the study	Until the end of the study	Until the end of the study
	Patients with progress during or after the bridging therapy who received as subsequent therapy ciltacel in the next line of treatment	Until Day 112 after ciltacel infusion[a]	Until the end of the study	Until the end of the study	Until the end of the study
	Patients with progress during or after the bridging therapy who did not receive ciltacel	Until 30 days after the last dose of the bridging therapy	Until 30 days after the last dose of the bridging therapy	Until the end of the study	-[b]
Control arm	Patients with progress during or after the bridging therapy who received as subsequent therapy ciltacel in the next line of treatment	Until 30 days after the last dose of the study medication or at the start of the subsequent therapy, whichever occurs first[a]	Until 30 days after the last dose of the study medication or at the start of the subsequent therapy, whichever occurs first[a]	Until the end of the study	-[b]

The data presented show that for patients in the control arm and patients in the intervention arm who did not receive treatment with ciltacabtagene autoleucel, the planned duration of follow-up observation of AEs, severe AEs and SAEs is systematically shortened compared to patients with CAR T cell infusion. Recordings up to the end of the study in both study arms as part of the AEs of special interest were planned for secondary malignancies only. In addition, observation of SAEs and the AEs of special interest “cytokine release syndrome” and “neurotoxicity” in the intervention arm was only planned for patients with CAR T cell infusion. With regard to these AEs of special interest, the company also describes that only AEs from the time of infusion were included in the predefined analysis provided for in the study design and that this analysis was intended exclusively for the intervention arm. In this regard, it points out that these AEs of special interest are presented by SOC and PT according to the Medical Dictionary for Drug Regulatory Activities (MedDRA) depending on the severity in the analyses, which include events as of the apheresis (intervention arm) or Day 1 of the study medication (comparator arm). In the company's view, suitable data are thus available for the assessment of these specific AEs by means of the SOC and PT analyses.

2.1.2.2 Sensitivity analyses on outcomes in the side effects category subsequently submitted by the company

In addition to the information on the recording of AEs within the framework of the CARTITUDE-4 study, the company presented sensitivity analyses on the outcomes in the side effects category, in which it considered different recording periods. Figure 3 provides an overview of the time periods considered in sensitivity analyses 1 and 2 depending on the assigned therapy and the course of treatment.

Studienarm	Patientenpopulation	Jegliche UE & Schwere UE ≥ Grad 3	Schwerwiegende UE
Ciltacel-Arm	Patienten ohne Progress während der Überbrückungstherapie, die Ciltacel als Studienmedikation erhalten haben	1. bis Tag 112 nach Ciltacel-Infusion 2. bis Tag 112 nach Ciltacel-Infusion oder Beginn einer Folgetherapie, je nachdem, was zuerst eintritt.	1. bis zum Studienende 2. bis zum Studienende oder Beginn einer Folgetherapie, je nachdem, was zuerst eintritt.
	Patienten mit Progress während oder nach der Überbrückungstherapie, die Ciltacel in der nächsten Therapielinie als Folgetherapie erhalten haben [a]	1. bis Tag 112 nach Ciltacel-Infusion 2. bis Tag 112 nach Ciltacel-Infusion oder Beginn einer Folgetherapie, je nachdem, was zuerst eintritt.	1. bis zum Studienende 2. bis zum Studienende oder Beginn einer Folgetherapie, je nachdem, was zuerst eintritt.
	Patienten mit Progress während oder nach der Überbrückungstherapie die kein Ciltacel erhalten haben	1. bis 30 Tage nach der letzten Dosis der Überbrückungstherapie 2. bis 30 Tage nach der letzten Dosis der Überbrückungstherapie oder Beginn einer Folgetherapie, je nachdem, was zuerst eintritt.	1. bis 30 Tage nach der letzten Dosis der Überbrückungstherapie 2. bis 30 Tage nach der letzten Dosis der Überbrückungstherapie oder Beginn einer Folgetherapie, je nachdem, was zuerst eintritt.
Kontrollarm		1 und 2: bis 30 Tage nach der letzten Dosis der Studienmedikation oder zum Beginn einer Folgetherapie, je nachdem, was zuerst eintritt	1 und 2: bis 30 Tage nach der letzten Dosis der Studienmedikation oder zum Beginn einer Folgetherapie, je nachdem, was zuerst eintritt

a: Für die Sensitivitätsanalysen wird im Interventionsarm die Behandlung mit Ciltacel auch im Falle einer Krankheitsprogression unter der Brückentherapie im Rahmen der aktuellen Therapielinie und nicht als Folgetherapie ausgewertet.

AE: adverse event; ciltacel: ciltacabtagene autoleucel

Figure 3: Recordings of AEs considered in sensitivity analyses 1 and 2 (taken from the company's comments)

Study arm	Patient population	Any AE and severe AE ≥ grade 3	Serious AEs
	Patients without progress under the bridging therapy who received ciltacel as study medication	1. Until Day 112 after ciltacel infusion 2. Until Day 112 after ciltacel infusion or initiation of a subsequent therapy, whichever occurs first	1. Until the end of the study 2. Until the end of the study or initiation of a subsequent therapy, whichever occurs first
	Patients with progress during or after the bridging therapy who received ciltacel as subsequent therapy in the next line of treatment	1. Until Day 112 after ciltacel infusion 2. Up to Day 112 after ciltacel infusion or initiation of a subsequent therapy, whichever occurs first	1. Until the end of the study 2. Until the end of the study or initiation of a subsequent therapy, whichever occurs first
	Patients with progress during or after the bridging therapy who did not receive ciltacel	1. Until 30 days after the last dose of bridging therapy 2. Until 30 days after the last dose of bridging therapy or initiation of a subsequent therapy, whichever occurs first	1. Until 30 days after the last dose of bridging therapy 2. Until 30 days after the last dose of bridging therapy or initiation of a subsequent therapy, whichever occurs first
Control arm		1 and 2: Until 30 days after the last dose of study medication or initiation of a subsequent therapy, whichever occurs first	1 and 2: Until 30 days after the last dose of study medication or initiation of a subsequent therapy, whichever occurs first
a: Also in the event of disease progression during bridging therapy, treatment with ciltacel in the intervention arm will be assessed as part of the current treatment line and not as subsequent therapy for the sensitivity analyses.			

According to the company, sensitivity analysis 1 includes the AEs per outcome up to the maximum observation period in which all events for the individual patients were completely recorded. If no event occurs in the corresponding observation periods, the patient is censored at the end of the observation period. The company stated that in addition to the maximum observation periods with complete recording of all events, the start of a subsequent therapy is taken into account for sensitivity analysis 2, depending on which occurs first. If no event occurs in the corresponding observation periods, the patient is censored at the end of the observation period or at the start of subsequent therapy, depending on which occurs first. Moreover, the company states that, deviating from the analyses presented in the dossier, in both analyses treatment with ciltacabtagene autoleucel in the intervention arm is assessed as part of the current line of treatment and not as subsequent therapy also in the event of disease progression during bridging therapy.

The information on the course of the study subsequently submitted by the company shows that, due to the additional censoring as of the administration of subsequent therapies in the intervention arm, there are only minor differences in the median observation durations for the individual outcomes between the two sensitivity analyses. For the majority of outcomes (with the exception of SAEs in the intervention arm), the observation period was significantly shorter than for the outcome of overall survival. In addition, as a consequence of the

differently planned duration of the follow-up observation, there are clear differences in the observation durations for the individual outcomes of the side effects category. The median observation period for sensitivity analysis 1 for AEs and severe AEs (CTCAE grade ≥ 3) is significantly shorter in the intervention arm at 6.3 months compared to the control arm at 12.2 months (sensitivity analysis 2: 6.2 months vs. 12.2 months). In sensitivity analysis 1, however, the median observation period for SAEs was significantly longer in the intervention arm than in the control arm (32.2 months vs. 12.2 months)(sensitivity analysis 2: 31.0 months vs. 12.2 months). Based on the available data, conclusions for outcomes in the side effects categories can only be drawn on these shortened observation periods.

For the benefit assessment, the analyses presented by the company as sensitivity analysis 1 that include AEs, SAEs and severe AEs up to the end of the maximum observation period are used, in which all events for the individual patients were completely recorded.

Sensitivity analysis 2 submitted by the company with additional censoring as of the administration of subsequent therapies in the intervention arm is presented as supplementary information in Appendix C.

2.1.2.3 Analyses on specific AEs

The company's dossier provides no suitable data for the specific AEs of cytokine release syndrome, severe neurological toxicity, infusion related reactions, severe infections and secondary malignancies. In particular, this was due to superordinate uncertainties regarding the recording of AEs in the CARTITUDE-4 study (see Section 2.1.2 for an explanation). These superordinate uncertainties were largely clarified with the analyses presented by the company in its comments. However, there are further points of criticism for the AEs of special interest, which are explained below.

Analyses of AEs of special interest not suitable for benefit assessment

Points of criticism remain for the AEs of special interest defined in the study design, so that the data on AEs of special interest from the CARTITUDE-4 study are still not suitable for the benefit assessment. This is due to the fact that it remains unclear to what extent the AEs of particular interest recorded in the study are systematically collected on the basis of a prespecified list of events to be recorded. With its comments, the company presented information on the individual System Organ Classes (SOCs) and Preferred Terms (PTs) on which the analyses of the AEs of particular interest are based. However, it should be noted that the data only represent a list of the events that occurred in the study. The data provided yield no information on whether there was a prespecified list of the SOCs/PTs that were to be recorded as AEs of special interest in the study. Moreover, with regard to the AEs "cytokine release syndrome" and "neurotoxicity", the company also describes that only AEs as of the time of infusion were included in the prespecified analysis provided for in the study design

and that this analysis was intended exclusively for the intervention arm (see Section 2.1.2.1). The analyses of AEs of special interest for the outcomes of cytokine release syndrome and neurotoxicity are therefore not included. For the outcome of secondary malignancies, only the operationalization via AEs of special interest is available in the CARTITUDE-4 study. As described above, however, it remains unclear to what extent these AEs were recorded systematically. For this reason, no suitable data for the benefit assessment are available for the outcome of secondary malignancies. Moreover, it should be noted that the observation period to date in the CARTITUDE-4 study may not be sufficient to fully represent secondary malignancies.

Suitable data on severe neurological toxicity and severe infections via analyses according to SOC/PT

With sensitivity analysis 1 subsequently submitted by the company, analyses on AEs, severe AEs (CTCAE grade ≥ 3) and SAEs as well as common AEs, common severe AEs (CTCAE grade ≥ 3) and common SAEs according to SOC/PT are available for the benefit assessment, each of which was systematically recorded. For the specific AEs “severe neurological toxicity” and “severe infections”, suitable data are available on the basis of these analyses in the form of the SOCs “nervous system disorders” and “infections and infestations”. These are accordingly used for the benefit assessment.

No suitable data on cytokine release syndrome and infusion related reactions

Based on the analyses of the CARTITUDE-4 study, there are still no suitable data available for the outcomes of cytokine release syndrome and infusion related reactions. This is due to the fact that the overlapping symptom complexes underlying these AEs (e.g. chills, fever or dyspnoea) were recorded differently in the two study arms.

The cytokine release syndrome, which frequently occurs in the context of CAR T cell therapy, was only specifically recorded in the intervention arm as an AE of special interest. According to the study planning, there were no specifications as to how the survey should be conducted. Based on the available results, however, it can be assumed that the survey was conducted via the PT cytokine release syndrome according to MedDRA. The underlying symptoms of cytokine release syndrome (e.g. chills), in contrast, were not documented separately and are therefore not included in the AE analyses according to SOC/PT. In contrast, infusion related reactions, which occur in particular during treatment with daratumumab in the control arm, were not specifically recorded in the study. Instead, in the control arm, the underlying symptoms were recorded via the individual PTs themselves, e.g. in the PT “fever”, in the PT “chills”, etc. Accordingly, when looking at the common AEs according to SOC/PT, 73% of patients in the intervention arm had at least 1 event in the PT “cytokine release syndrome”, while only 1 patient in the comparator arm had at least 1 event (see Table 6 in Appendix B).

Due to the difference in data recordings between the intervention and comparator arms, no conclusions can be drawn regarding the outcomes of cytokine release syndrome and infusion related reactions. To make it possible to obtain meaningful data on these outcomes for the benefit assessment in unblinded studies comparing drugs that can induce either a cytokine release syndrome or an infusion related reaction, an aggregated analysis of all symptomatic AEs potentially relevant for the cytokine release syndrome and the infusion related reactions (e.g. chills, fever or dyspnoea) is necessary. Specific AEs that represent a cytokine release syndrome and/or infusion related reactions should either be predefined or refer to content-based compilations based on publications or compilations of the MedDRA system (e.g. a PT list) and should be recorded in both study arms. Irrespective of such an aggregated analysis (e.g. using a PT list), it is necessary that the individual symptoms underlying the cytokine release syndrome or the infusion related reactions are included in the general analysis of AEs according to SOC/PT.

For specific AEs that reflect the underlying overlapping symptom complexes of the cytokine release syndrome and the infusion related reactions, there is uncertainty due to the differing data recordings in the intervention arm (via PT “cytokine release syndrome”) and the control arm (via PTs on individual symptoms). In the present data situation, however, it is not assumed for severe AEs (CTCAE grade ≥ 3) and SAEs that this has an effect on the analyses according to SOC/PT, as only a few severe or serious events were recorded in the PT “cytokine release syndrome”. For the analyses of any AE according to SOC/PT, however, it can be assumed that events that are covered by the underlying overlapping symptom complex, such as chills or fever are associated with a high degree of uncertainty. This issue has been taken into account in the assessment of the risk of bias of specific AEs according to SOC/PT (see Section 2.1.3).

2.1.3 Risk of bias

The risk of bias for the results on the outcomes of the side effects category was rated as high. This is because the reasons that lead to a discontinuation of observation are potentially informative for the occurrence of events in these outcomes. In the present data situation, this results not only from the fact that the observation is linked to the end of treatment, but also from the fact that in the intervention arm, the complete observation of all AEs or SAEs for the individual patient (in different ways depending on the outcome) depended on the course of treatment, i.e. the administration of the CAR T cell infusion. According to the study design, this period also differs between the intervention and comparator arm. For a detailed explanation of the maximum observation period taken into account in the analyses, during which all events were recorded for the individual patients, see Section 2.1.2.2.

For specific AEs that represent the underlying overlapping symptom complexes of the cytokine release syndrome and infusion related reactions, there is also a high risk of bias in the results, as these were recorded differently in the intervention and the control arm of the study (see

Section 2.1.2.3). In the present data situation, however, based on the frequency of events in the PT “cytokine release syndrome” occurring in the study, it is assumed that this only affects the analyses of any AEs according to SOC/PT. It cannot be excluded with sufficient certainty that further differences to the disadvantage of the intervention would arise if the underlying symptoms had been recorded in the individual PTs. In the present data situation, however, it is not assumed that this has a relevant impact on the conclusion of the benefit assessment. For the results of non-serious/non-severe AEs, the risk of bias is additionally increased due to lack of blinding in the presence of subjective outcome recording.

2.1.4 Results

The results of sensitivity analysis 1 on the outcomes in the side effects category presented by the company with the comments are shown in Table 1. Kaplan-Meier curves for the presented time-to-event analyses based on sensitivity analysis 1 can be found in Appendix A, results for common AEs, SAEs and severe AEs based on sensitivity analysis 1 can be found in Appendix B.

Table 1: Results (side effects) – RCT, direct comparison: ciltacabtagene autoleucel versus individualized treatment, choosing from daratumumab in combination with pomalidomide and dexamethasone (DPd) or pomalidomide in combination with bortezomib and dexamethasone (PVd) (multipage table)

Study **outcome category** **outcome**	**Ciltacabtagene autoleucel**		**Individualized treatment choosing from DPd or PVd**		**Ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd**
	N	**median time to event in months [95% CI]** **patients with event n (%)**	**N**	**median time to event in months [95% CI]** **patients with event n (%)**	**HR [95% CI]; p-value[a]**
CARTITUDE-4					
Side effects					
AEs (supplementary information)	208	0.20 [0.13; 0.26] 208 (100)	208	0.13 [0.07; 0.20] 208 (100)	–
SAEs	208	9.86 [5.62; 15.57] 139 (66.8)	208	19.48 [12.42; 25.23] 99 (47.6)	1.25 [0.96; 1.63]; 0.103
Severe AEs[b]	208	0.72 [0.56; 0.76] 203 (97.6)	208	0.69 [0.49; 0.72] 202 (97.1)	0.93 [0.75; 1.14]; 0.455
Cytokine release syndrome	No suitable data[c]				
Severe neurological toxicity[d]	208	NA 26 (12.5)	208	NA 6 (2.9)	3.38 [1.38; 8.29]; 0.008
Infusion related reactions	No suitable data[c]				
Severe infections[e]	208	NA [31.57; NC] 84 (40.4)	208	NA [24.81; NC] 63 (30.3)	0.95 [0.68; 1.34]; 0.779
Secondary malignancies	No suitable data[c]				
Other specific AEs					
Headache (PT, AEs)	208	NA 58 (27.9)	208	NA 27 (13.0)	3.09 [1.87; 5.10]; < 0.001
Insomnia (PT, AEs)	208	NA 23 (11.1)	208	NA 55 (26.4)	0.43 [0.26; 0.70]; < 0.001

Table 1: Results (side effects) – RCT, direct comparison: ciltacabtagene autoleucel versus individualized treatment, choosing from daratumumab in combination with pomalidomide and dexamethasone (DPd) or pomalidomide in combination with bortezomib and dexamethasone (PVd) (multipage table)

Study outcome category outcome	Ciltacabtagene autoleucel		Individualized treatment choosing from DPd or PVd		Ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value[a]
Thrombocytopenia (PT, severe AEs[b])	208	NA [5.95; NC] 89 (42.8)	208	NA 41 (19.7)	2.49 [1.70; 3.64]; < 0.001
Anaemia (PT, severe AEs[b])	208	NA 80 (38.5)	208	NA 33 (15.9)	2.88 [1.90; 4.37]; < 0.001
Lymphopenia (PT, severe AEs[b])	208	NA 46 (22.1)	208	NA 25 (12.0)	2.02 [1.22; 3.33]; 0.006
Leukopenia (PT, severe AEs[b])	208	NA 27 (13.0)	208	NA 10 (4.8)	2.75 [1.33; 5.69]; 0.006
Metabolism and nutrition disorders (SOC, severe AEs[b])	208	NA 33 (15.9)	208	NA 15 (7.2)	2.47 [1.30; 4.69]; 0.006
Hypogammaglobulinaemia (PT, severe AEs[b])	208	NA [8.02; NC] 12 (5.8)	208	NA 2 (1.0)	52.86 [5.41; 516.19]; < 0.001

a. Since the company did not provide any information, it is assumed that the analysis methods correspond to those from Module 4 A [4]: HR, CI and p-value: Cox proportional hazards model, stratified by comparator therapy of investigator's choice (DPd vs. PVd), ISS stage (I vs. II vs. III) and number of prior lines of therapy (1 vs. 2 or 3).
b. Operationalized as CTCAE grade ≥ 3.
c. See Section 2.1.2.3 for reasons.
d. Operationalized as SAEs of the SOC “nervous system disorders”.
e. Operationalized as SAEs of the SOC “infections and infestations”.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; DPd: daratumumab in combination with pomalidomide and dexamethasone; HR: hazard ratio; ISS: International Staging System; n: number of patients with (at least 1) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; PVd: pomalidomide in combination with bortezomib and dexamethasone; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

On the basis of the available information, no more than hints, e.g. of an added benefit, can be determined for all outcomes.

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 from ciltacabtagene autoleucel in comparison with individualized treatment selecting from DPd or PVd. Greater or lesser harm is therefore not proven for these outcomes.

Specific AEs

Cytokine release syndrome, infusion related reactions and secondary malignancies

No suitable data are available for each of the outcomes of cytokine release syndrome, infusion related reactions and secondary malignancies (see Section 2.1.2.3 for reasons). In each case, there is no hint of greater or lesser harm from ciltacabtagene autoleucel in comparison with individualized treatment selecting from DPd or PVd. Greater or lesser harm is therefore not proven for these outcomes.

Severe neurological toxicity (SAEs)

A statistically significant difference to the disadvantage of ciltacabtagene autoleucel in comparison with individualized treatment choosing from DPd or PVd was shown for the outcome of severe neurological toxicity (SAEs). There is a hint of greater harm from ciltacabtagene autoleucel in comparison with individualized treatment choosing from DPd or PVd for this outcome.

Severe infections (SAEs)

No statistically significant difference between treatment groups was shown for the outcome of severe infections. There is no hint of greater or lesser harm from ciltacabtagene autoleucel in comparison with individualized treatment selecting from DPd or PVd. Greater or lesser harm is therefore not proven for this outcome.

Headache (AEs)

A statistically significant difference to the disadvantage of ciltacabtagene autoleucel in comparison with individualized treatment choosing from DPd or PVd was shown for the outcome of headache (AEs). There is a hint of greater harm from ciltacabtagene autoleucel in comparison with individualized treatment choosing from DPd or PVd for the outcome of headache (AEs).

Insomnia (AEs)

A statistically significant difference in favour of ciltacabtagene autoleucel in comparison with individualized treatment choosing from DPd or PVd was shown for the outcome of insomnia (AEs). There is a hint of lesser harm from ciltacabtagene autoleucel in comparison with individualized treatment choosing from DPd or PVd for the outcome of insomnia (AEs).

Thrombocytopenia (severe AEs), lymphopenia (severe AEs), leukopenia (severe AEs) and hypogammaglobulinaemia (severe AEs)

A statistically significant difference to the disadvantage of ciltacabtagene autoleucel in comparison with individualized treatment choosing from DPd or PVd was shown for each of the outcomes of thrombocytopenia (severe AEs), lymphopenia (severe AEs), leukopenia (severe AEs) and hypogammaglobulinaemia (severe AEs). There is a hint of greater harm from ciltacabtagene autoleucel in comparison with individualized treatment choosing from DPd or PVd for the outcomes of thrombocytopenia" (severe AEs), lymphopenia (severe AEs), leukopenia (severe AEs) and hypogammaglobulinaemia (severe AEs).

Anaemia (severe AEs)

A statistically significant difference to the disadvantage of ciltacabtagene autoleucel in comparison with individualized treatment choosing from DPd or PVd was shown for the outcome of anaemia (severe AEs). There is an effect modification by the characteristic of sex for this outcome (see Section 2.1.5). A statistically significant difference to the disadvantage of ciltacabtagene autoleucel in comparison with individualized treatment choosing from DPd or PVd was shown both for women and men. Thereby, the extent of the effect differs between the subgroups. For this outcome, there is a hint of greater harm from ciltacabtagene autoleucel in comparison with individualized treatment choosing from DPd or PVd both for women and men.

Metabolism and nutrition disorders (severe AEs)

A statistically significant difference to the disadvantage of ciltacabtagene autoleucel in comparison with individualized treatment choosing from DPd or PVd was shown for the outcome of metabolism and nutrition disorders (severe AEs). There is an effect modification by the characteristic of age for this outcome (see Section 2.1.5). There is a hint of greater harm from ciltacabtagene autoleucel in comparison with individualized treatment choosing from DPd or PVd for patients ≥ 65 years. For patients < 65 years, there is no hint of greater or lesser harm from ciltacabtagene autoleucel in comparison with individualized treatment choosing from DPd or PVd; greater or lesser harm is therefore not proven for these patients.

2.1.5 Subgroups and other effect modifiers

The following characteristics were considered to be relevant in the present benefit assessment (see dossier assessment A24-116):

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

The methods described in Section I 4.4 of dossier assessment A24-116 are used.

The results are presented in Table 2. The Kaplan-Meier curves on the event time analyses are presented in Appendix A.1 of the full dossier assessment.

Table 2: Subgroups – RCT, direct comparison: ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd

Study outcome characteristic subgroup	Ciltacabtagene autoleucel		Individualized treatment choosing from DPd or PVd		Ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd	
	N	median time to event in months [95 % CI] patients with event n (%)	N	median time to event in months [95 % CI] patients with event n (%)	HR [95% CI][a]	p-value[a]
CARTITUDE-4						
Anaemia (PT, severe AEs[b])						
Sex						
Female	92	NA [2.96; NC] 45 (48.9)	86	NA 12 (14.0)	5.09 [2.56; 10.10]	< 0.001
Male	116	NA 35 (30.2)	122	NA 21 (17.2)	1.75 [1.02; 3.00]	0.044
Total					Interaction:	0.036
Metabolism and nutrition disorders (SOC, severe AEs[b])						
Age						
< 65 years	126	NA 20 (15.9)	129	NA 14 (10.9)	1.67 [0.82; 3.40]	0.162
≥ 65 years	82	NA 13 (15.9)	79	NA 1 (1.3)	12.53 [1.64; 95.76]	0.015
Total					Interaction:	0.046

a. Since the company did not provide any information on the analysis methods, it is assumed that this corresponds to that from Module 4 A [4]: HR, CI and p-value: Cox PH model, unstratified; interaction p-value: Cox PH model with treatment arm, subgroup characteristic and interaction term for treatment and subgroup characteristic.
b. 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; HR: hazard ratio; n: number of patients with at least 1 event; N: number of analysed patients; PT: Preferred Term; PVd: pomalidomide in combination with bortezomib and dexamethasone; RCT: randomized controlled trial; SOC: System Organ Class

Side effects

Anaemia (severe AEs)

There was an effect modification by the characteristic of sex for the outcome of anaemia (severe AEs). A statistically significant difference to the disadvantage of ciltacabtagene autoleucel in comparison with individualized treatment choosing from DPd or PVd was shown both for women and men. The extent of the effect differs between the subgroups. There is a hint of greater harm from ciltacabtagene autoleucel in comparison with individualized treatment choosing from DPd or PVd both for women and men.

Metabolism and nutrition disorders (severe AEs)

For the outcome of metabolism and nutrition disorders (severe AEs), there is an effect modification by the characteristic of age. A statistically significant difference to the disadvantage of ciltacabtagene autoleucel was found for patients ≥ 65 years, whereas no statistically significant difference between treatment groups was shown for patients < 65 years of age. There is a hint of greater harm from ciltacabtagene autoleucel in comparison with individualized treatment choosing from DPd or PVd for patients ≥ 65 years. For patients < 65 years, there is no hint of greater or lesser harm from ciltacabtagene autoleucel in comparison with individualized treatment choosing from DPd or PVd; greater or lesser harm is therefore not proven for these patients.

2.2 Probability and extent of added benefit

2.2.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in dossier assessment A24-116 and the previous sections (see Table 3).

Table 3: Extent of added benefit at outcome level: ciltacabtagene autoleucel vs. individualized treatment[a] (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd** **median time to event (months)** **HR [95% CI];** **p-value** **probability[b]**	**Derivation of extent[c]**
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	NA vs. NA 0.55 [0.39; 0.79]; p < 0.001 probability: "hint"	Outcome category: mortality CI_u < 0.85 added benefit, extent: "major"
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC QLQ C30, PGIS, MySIm-Q Total Symptom Score)	No suitable data	Lesser/added benefit not proven
Health status (EQ-5D VAS)	No suitable data	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30, MySIm-Q Total Impact Score	No suitable data	Lesser/added benefit not proven
Side effects		
SAEs	9.86 vs. 19.48 1.25 [0.96; 1.63]; p = 0.103	Greater/lesser harm not proven
Severe AEs	0.72 vs. 0.69 0.93 [0.75; 1.14]; p = 0.455	Greater/lesser harm not proven
Discontinuation due to AEs	NA vs. NA 0.47 [0.18; 1.21]; p = 0.116	Greater/lesser harm not proven
PRO-CTCAE	No suitable data	Greater/lesser harm not proven
Cytokine release syndrome	No suitable data	Greater/lesser harm not proven
Severe neurological toxicity (SAEs)	NA vs. NA 3.38 [1.38; 8.29]; 0.30 [0.12; 0.73][d]; p = 0.008 Probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% Greater harm, extent: "major"
Infusion related reactions	No suitable data	Greater/lesser harm not proven

Table 3: Extent of added benefit at outcome level: ciltacabtagene autoleucel vs. individualized treatment[a] (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd** **median time to event (months)** **HR [95% CI];** **p-value** **probability[b]**	**Derivation of extent[c]**
Severe infections (SAEs)	NA vs. NA 0.95 [0.68; 1.34]; p = 0.779	Greater/lesser harm not proven
Secondary malignancies	No suitable data	Greater/lesser harm not proven
Headache (AEs)	NA vs. NA 3.09 [1.87; 5.10]; 0.32 [0.20; 0.54][d]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: "considerable"
Insomnia (AEs)	NA vs. NA 0.43 [0.26; 0.70]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: "considerable"
Thrombocytopenia (severe AEs)	NA vs. NA 2.49 [1.70; 3.64]; 0.40 [0.27; 0.59][d]; p < 0.001 probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% greater harm, extent: "major"
Anaemia (severe AEs) Sex Female	NA vs. NA 5.09 [2.56; 10.10]; 0.20 [0.10; 0.39][d]; p < 0.001 probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% greater harm, extent: "major"
Male	NA vs. NA 1.75 [1.02; 3.00]; 0.57 [0.33; 0.98][d]; p = 0.044 probability: "hint"	Outcome category: serious/severe side effects 0.90 ≤ CI_u < 1.00 greater harm, extent: "minor"
Lymphopenia (severe AEs)	NA vs. NA 2.02 [1.22; 3.33]; 0.50 [0.30; 0.82][d]; p = 0.006 probability: "hint"	Outcome category: serious/severe side effects 0.75 ≤ CI_u < 0.90 greater harm, extent: "considerable"

Table 3: Extent of added benefit at outcome level: ciltacabtagene autoleucel vs. individualized treatment[a] (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd** **median time to event (months)** **HR [95% CI];** **p-value** **probability[b]**	**Derivation of extent[c]**
Leukopenia (severe AEs)	NA vs. NA 2.75 [1.33; 5.69]; 0.36 [0.18; 0.7502][d]; p = 0.006 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"
Metabolism and nutrition disorders (severe AEs) Age		
< 65 years	NA vs. NA 1.67 [0.82; 3.40]; p = 0.162	Greater/lesser harm not proven
≥ 65 years	NA vs. NA 12.53 [1.64; 95.76]; 0.08 [0.01; 0.61][d]; p = 0.015 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% greater harm, extent: "major"
Hypogammaglobulinaemia (severe AEs)	NA vs. NA 52.86 [5.41; 516.19]; 0.02 [0.00; 0.18][d]; p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% greater harm, extent: "major"

a. In the CARTITUDE-4 study, the investigators could choose from the drug combinations DPd and PVd.
b. Probability provided if a statistically significant and relevant effect is present.
c. Depending on the outcome category, estimations of effect size use different limits based on the upper limit of the confidence interval (CI_u).
d. Institute's calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; DPd: daratumumab in combination with pomalidomide and dexamethasone; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; MySIm-Q: Multiple Myeloma Symptom and Impact Questionnaire; NA: not achieved; PGIS: Patient Global Impression of Severity; PRO-CTCAE: Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; PVd: pomalidomide in combination with bortezomib and dexamethasone; QLQ-C30: Quality of Life Questionnaire - Core 30; SAE: serious adverse event; VAS: visual analogue scale

2.2.2 Overall conclusion on added benefit

Table 4 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 4: Positive and negative effects from the assessment of ciltacabtagene autoleucel compared with individualized treatment[a]

Positive effects	Negative effects
Outcomes with observation over the entire study duration	
Mortality ▪ overall survival: hint of an added benefit – extent: "major"	–
Outcomes with shortened observation period	
–	Serious/severe side effects ▪ severe neurological toxicity (SAEs): hint of greater harm – extent: "major" ▪ thrombocytopenia (severe AEs): hint of greater harm – extent: "major" ▪ anaemia (severe AEs): ▫ sex female: hint of greater harm – extent: "major" ▫ Sex male: hint of greater harm – extent "minor" ▪ lymphopenia (severe AEs): hint of greater harm – extent: "considerable" ▪ leukopenia (severe AEs): hint of greater harm – extent: "considerable" ▪ metabolism and nutrition disorders (severe AEs): ▫ Age ≥ 65 years: hint of greater harm – extent: "major" ▪ hypogammaglobulinaemia (severe AEs): hint of greater harm – extent: "major"
Non-serious/non-severe side effects ▪ insomnia (AEs): hint of lesser harm – extent: "considerable"	Non-serious/non-severe side effects ▪ headache (AEs): hint of greater harm - extent: "considerable"
No suitable data are available for the outcome categories of morbidity (EORTC QLQ-C30, PGIS, EQ 5D VAS, MySIm-Q Total Symptom Score) and health-related quality of life (EORTC QLQ-C30, MySIm-Q Total Impact Score) as well as the outcomes PRO-CTCAE, cytokine release syndrome, infusion-related reactions and secondary malignancies.	
a. In the CARTITUDE-4 study, the investigators could choose from the drug combinations DPd and PVd. AE: adverse event; DPd: daratumumab in combination with pomalidomide and dexamethasone; EORTC: European Organisation for Research and Treatment of Cancer; MySIm-Q: Multiple Myeloma Symptom and Impact Questionnaire; PGIS: Patient Global Impression of Severity; PRO-CTCAE: Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; PVd: pomalidomide in combination with bortezomib and dexamethasone; QLQ-C30: Quality of Life Questionnaire - Core 30; SAE: serious adverse event; VAS: visual analogue scale	

In comparison with dossier assessment A24-116, further results for the side effects category are now available for the benefit assessment.

The overall picture shows a hint of an added benefit with the extent “considerable” for overall survival. In contrast, the disadvantages of ciltacabtagene autoleucel are shown in the case of serious/severe side effects, mostly also to a major extent. Moreover, no suitable data are available for the benefit assessment for outcomes in the categories of morbidity and health-related quality of life as well as individual specific AEs relevant in the present treatment situation. The disadvantages for outcomes in the side effects category do not completely challenge the advantage in overall survival, but lead to a downgrading of the extent of the added benefit overall.

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

2.3 Summary

The data subsequently submitted by the company in the commenting procedure change the conclusion on the added benefit of ciltacabtagene autoleucel from dossier assessment A24-116 for adult patients with relapsed and refractory multiple myeloma who have previously received 1 to 3 prior therapies, including 1 immunomodulator and 1 proteasome inhibitor, and who demonstrated disease progression on the last therapy and are refractory to lenalidomide, and for whom DPd or PVd is a suitable individualized treatment.

For adult patients with relapsed and refractory multiple myeloma who have previously received 1 to 3 prior therapies, including 1 immunomodulator and 1 proteasome inhibitor, and who demonstrated disease progression on the last therapy and are refractory to lenalidomide, and for whom DPd or PVd is not a suitable individualized treatment as well as for patients who have already received at least 4 prior therapies, there is no change in comparison with dossier assessment A24-116.

The following Table 5 shows the result of the benefit assessment of ciltacabtagene autoleucel taking into account both dossier assessment A24-116 and the present addendum.

Table 5: Ciltacabtagene autoleucel – probability and extent of added benefit (multipage table)

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

Table 5: Ciltacabtagene autoleucel – probability and extent of added benefit (multipage table)

Therapeutic indication	ACT[a]	Probability and extent of added benefit
a. Presented is the ACT specified by the G-BA. b. For the implementation of individualized treatment in a study of direct comparison, the investigators are expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons). c. According to the G-BA, the duration of response to the prior therapy is a criterion for the individualized treatment. In this respect, according to the generally recognized state of medical knowledge, unsuitability of retreatment with the drugs or drug combinations of the prior therapy is defined as disease progression under the respective prior therapy or a duration of response of less than 12 months after completion of the respective prior therapy. Accordingly, for patients with relapsed disease who show a response in the form of CR, VGPR and PR of more than 12 months after completion of the prior therapy, treatment using the drugs or drug combinations used in the prior therapy may also be a suitable treatment option. d. Only for patients with at least 2 prior therapies. e. Only for patients who are refractory to a CD38 antibody. f. Only for patients who have received at least 4 prior therapies. g. Only for at least double-refractory patients for whom triplet therapy is not suitable. h. Only for at least triple-refractory patients for whom triplet or doublet therapy is not suitable. i. Only for patients after 1 prior therapy for whom autologous stem cell transplantation is an option; after achieving remission. Autologous stem cell transplantation should be offered to all patients eligible for transplantation who have not undergone transplantation as part of first-line therapy. In addition, an autologous re-transplantation can be performed if the progression-free survival after the first transplantation generally lasted at least 18 months. j. Only for patients after 1 prior therapy for whom allogeneic stem cell transplantation is an option; after achieving remission. Allogeneic stem cell transplantation is a treatment option for patients with primary refractoriness and an early relapse after autologous stem cell transplantation. k. The requirements of the "G-BA guideline on the testing of allogeneic stem cell transplantation in multiple myeloma beyond first-line therapy" Gemeinsamer Bundesausschuss, 2017 #29}, the "G-BA's decision on measures of quality assurance for allogeneic stem cell transplantation in multiple myeloma (QS-B SZT MM)" [5] and §137c of the German Social Code Book V shall apply with regard to the use of allogeneic stem cell transplantation. l. According to the G-BA, unsuitability of triplet or doublet therapy should be justified based on refractoriness and comorbidity of the patients and taking into account the toxicity of the respective therapy. m. According to the G-BA, patients in the present therapeutic indication are assumed to generally continue antineoplastic treatment. Best supportive care is therefore not considered an ACT. o. The CARTITUDE-4 study included only patients with an ECOG PS of 0 or 1. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2. DPd: daratumumab in combination with pomalidomide and dexamethasone; ECOG-PS: Eastern Cooperative Oncology Group – Performance Status; G-BA: Federal Joint Committee; CD: cluster of differentiation; CR: complete response; PR: partial response; PVd: pomalidomide in combination with bortezomib and dexamethasone; SGB: Social Code Book; VGPR: very good partial response		

The G-BA decides on the added benefit.

3 References

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

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Ciltacabtagene Autoleucel (multiples Myelom); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2025 [Accessed: 04.03.2025]. URL: https://doi.org/10.60584/A24-116.

2. Johnson & Johnson. Stellungnahme zum IQWiG-Bericht Nr. 1942: Ciltacabtagene Autoleucel (multiples Myelom); Nutzenbewertung gemäß § 35a SGB V. 2025: [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1088/#beschluesse in the document "Zusammenfassende Dokumentation"].

3. Johnson & Johnson. Anlage zur Stellungnahme zum IQWiG-Bericht Nr. 1942: Ciltacabtagene Autoleucel (multiples Myelom); Nutzenbewertung gemäß § 35a SGB V [unpublished]. 2025.

4. Johnson & Johnson. Ciltacabtagene Autoleucel (CARVYKTI); Dossier zur Nutzenbewertung gemäß § 35a SGB V; Modul 4 A [online]. 2024 [Accessed: 13.03.2025]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1088/#dossier.

5. Gemeinsamer Bundesausschuss. Maßnahmen zur Qualitätssicherung der allogenen Stammzelltransplantation bei Multiplem Myelom sowie eine Änderung der MD-Qualitätskontroll-Richtlinie [online]. 2022 [Accessed: 13.01.2025]. URL: https://www.g-ba.de/beschluesse/5691/.

Appendix A Kaplan-Meier curves (sensitivity analysis 1)

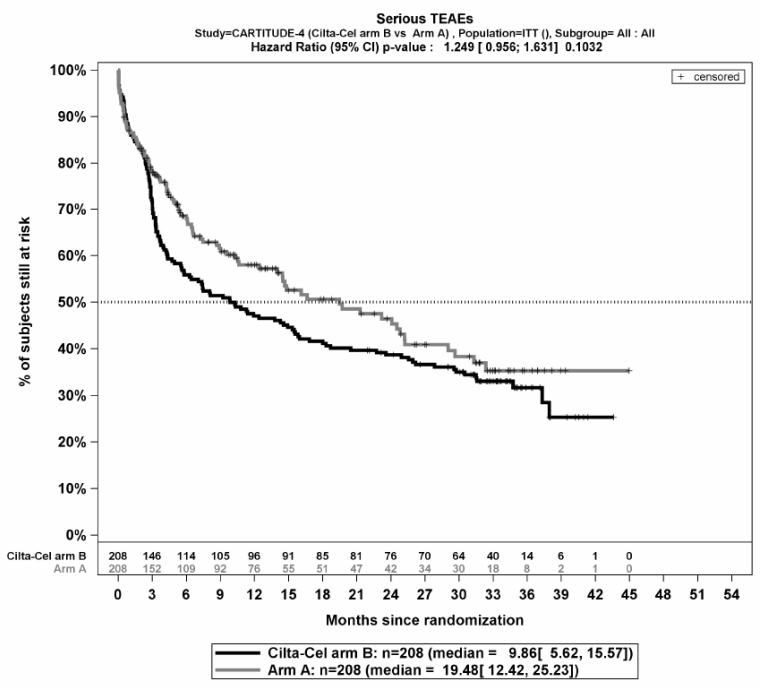

Figure 4: Kaplan-Meier curves for the outcome of SAEs, CARTITUDE-4 study, sensitivity analysis 1, data cut-off from 01 May 2024

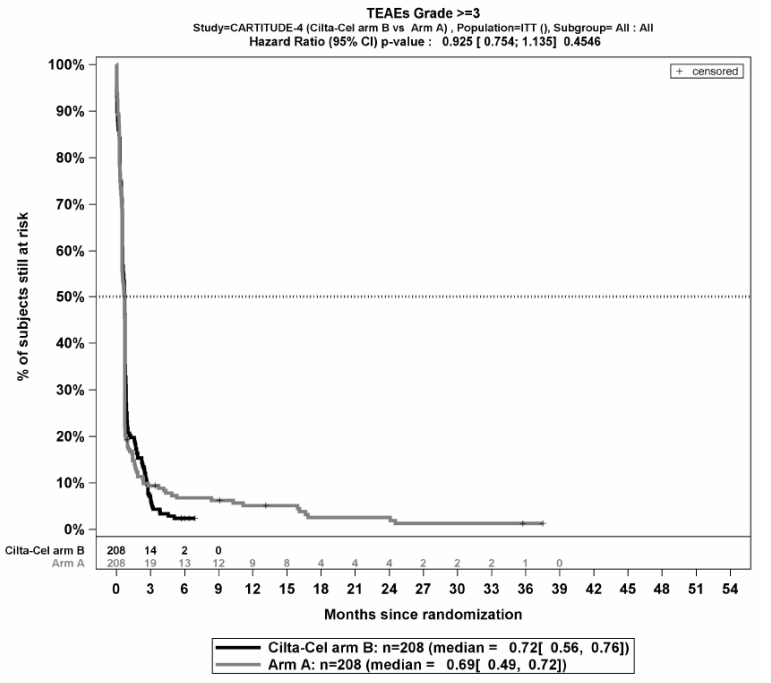

Figure 5: Kaplan-Meier curves for the outcome of severe AEs, CARTITUDE-4 study, sensitivity analysis 1, data cut-off from 1 May 2024

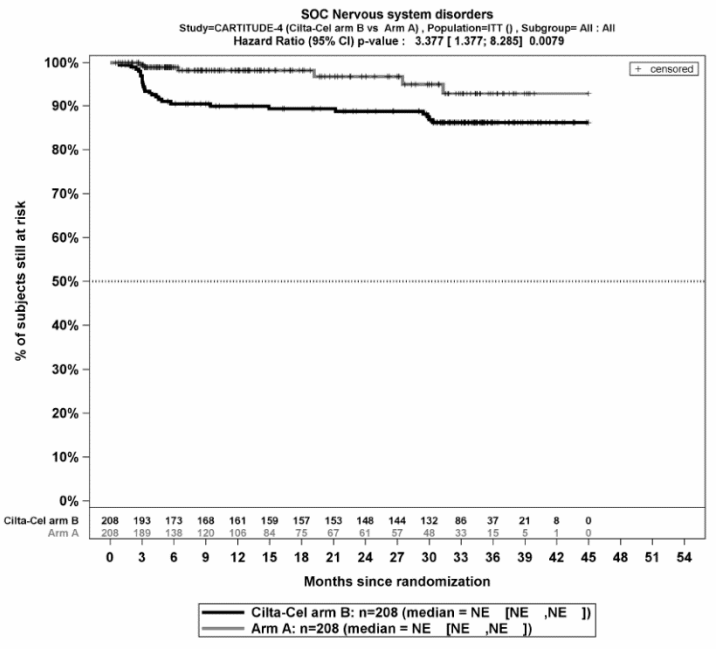

Figure 6: Kaplan-Meier curves for the outcome of severe neurological toxicity (operationalized via SAEs of the SOC "nervous system disorders"), CARTITUDE-4 study, sensitivity analysis 1, data cut-off from 01 May 2024

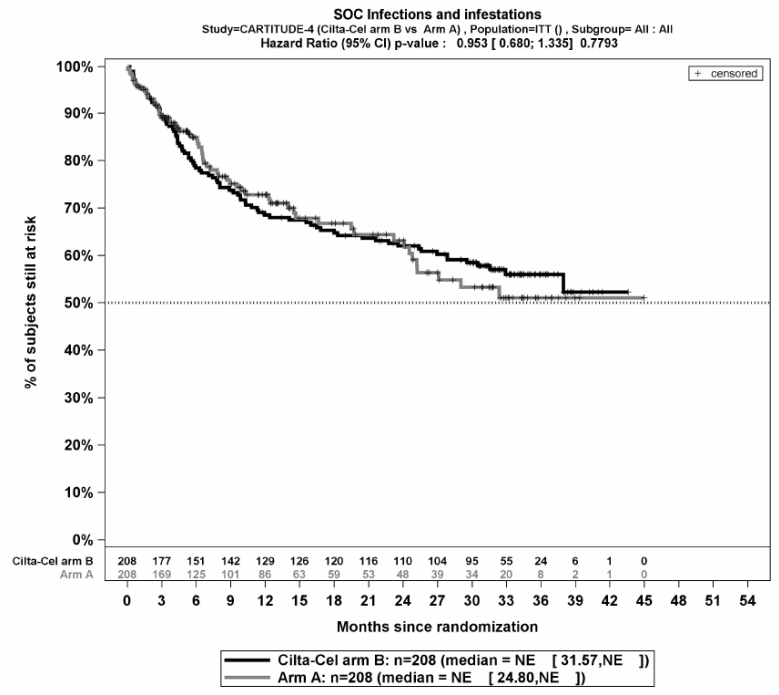

Figure 7: Kaplan-Meier curves for the outcome of severe infections (operationalized via SAEs of the SOC "infections and infestations"), CARTITUDE-4 study, sensitivity analysis 1, data cut from 1 May 2024

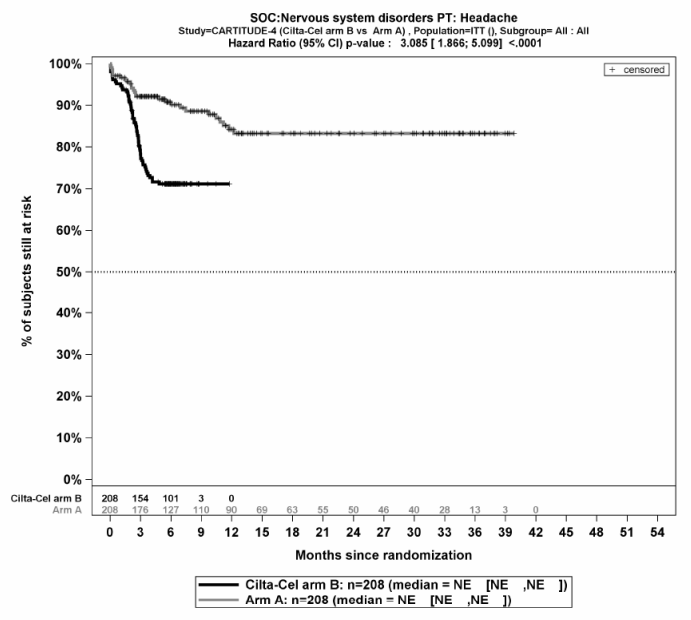

Figure 8: Kaplan-Meier curves for the outcome of headache (PT, AEs), CARTITUDE-4 study, sensitivity analysis 1, data cut-off from 1 May 2024

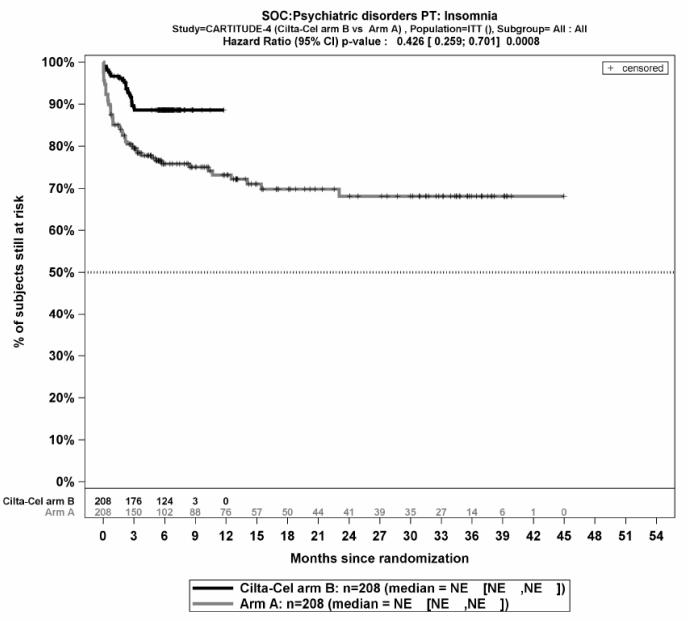

Figure 9: Kaplan-Meier curves for the outcome of insomnia (PT, AEs), CARTITUDE-4 study, sensitivity analysis 1, data cut-off from 1 May 2024

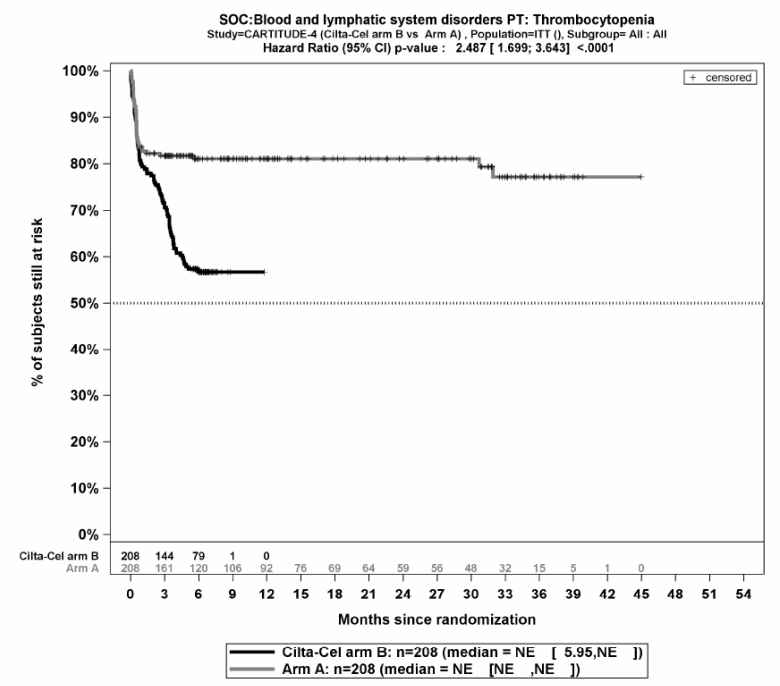

Figure 10: Kaplan-Meier curves for the outcome of thrombocytopenia (PT, severe AEs), CARTITUDE-4 study, sensitivity analysis 1, data cut-off from 1 May 2024

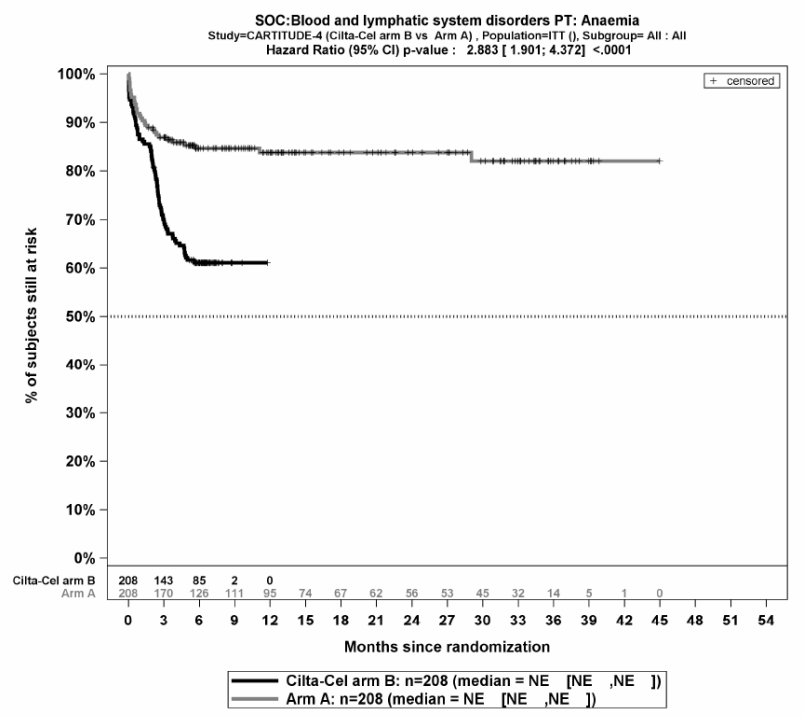

Figure 11: Kaplan-Meier curves for the outcome of anaemia (PT, severe AEs), CARTITUDE-4 study, sensitivity analysis 1, data cut-off from 1 May 2024

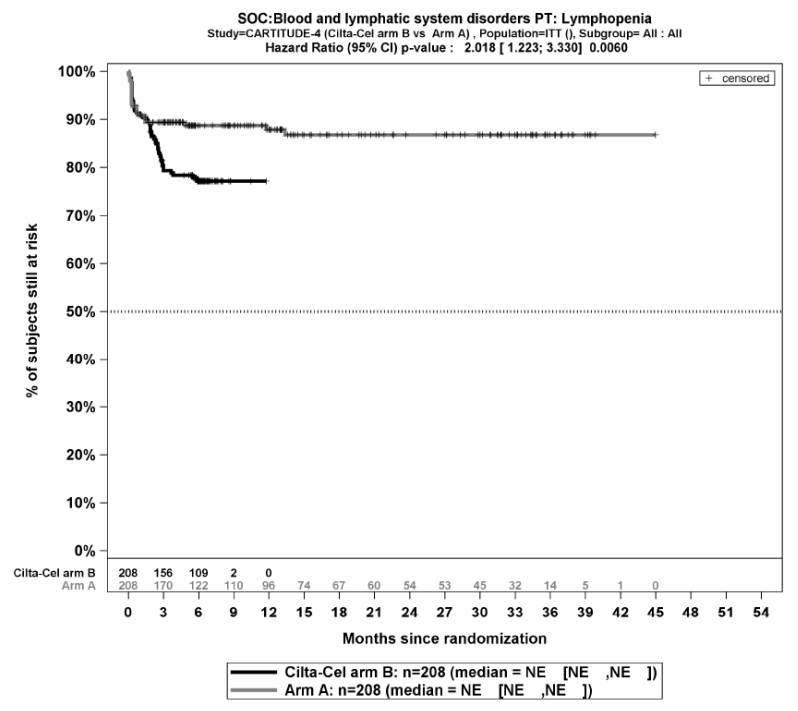

Figure 12: Kaplan-Meier curves for the outcome of lymphopenia (PT, severe AEs), CARTITUDE-4 study, sensitivity analysis 1, data cut-off from 1 May 2024

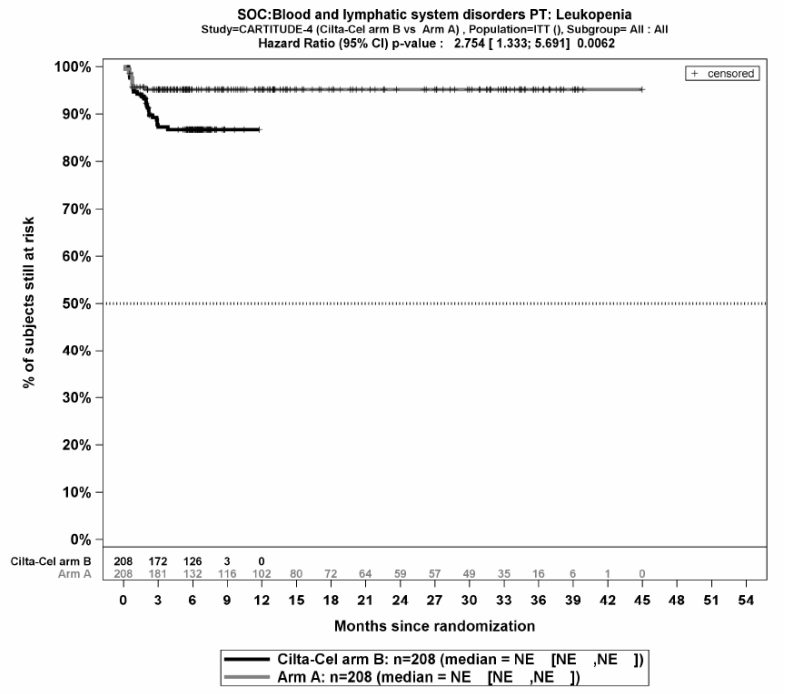

Figure 13: Kaplan-Meier curves for the outcome of leukopenia (PT, severe AEs), CARTITUDE-4 study, sensitivity analysis 1, data cut-off from 1 May 2024

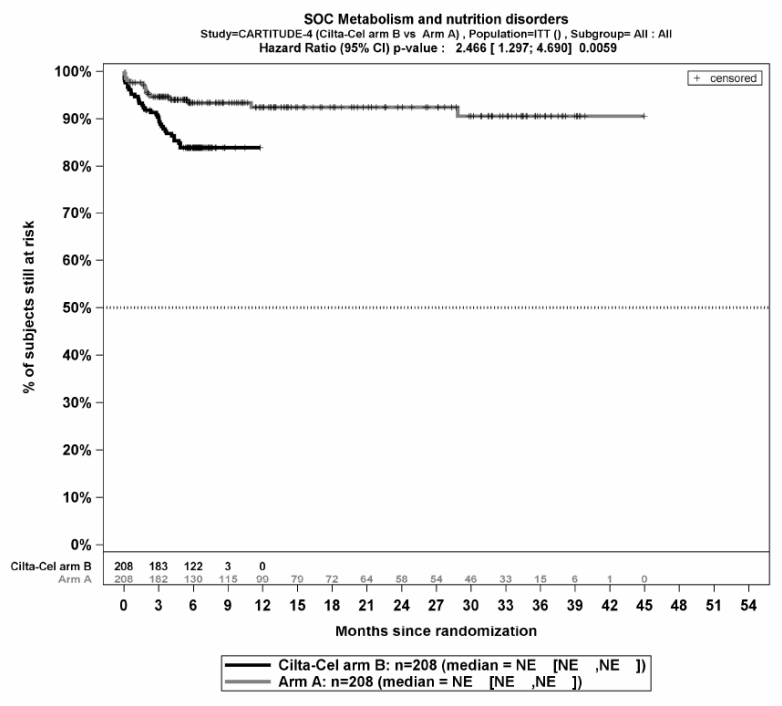

Figure 14: Kaplan-Meier curves for the outcome of metabolism and nutrition disorders (SOC, severe AEs), CARTITUDE-4 study, sensitivity analysis 1, data cut-off from 1 May 2024

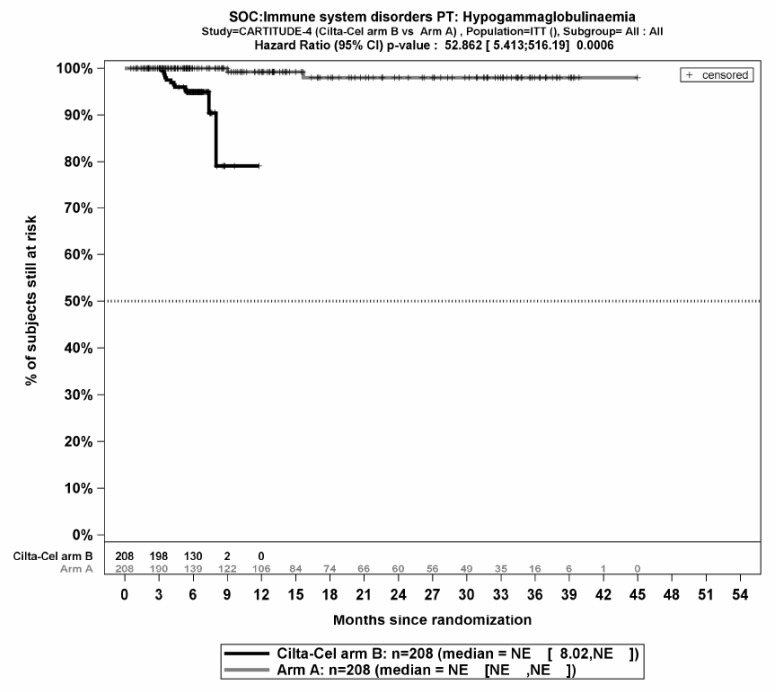

Figure 15: Kaplan-Meier curves for the outcome of hypogammaglobulinaemia (PT, severe AEs), CARTITUDE-4 study, sensitivity analysis 1, data cut-off from 1 May 2024

Kaplan-Meier curves on subgroups analyses

Anaemia (PT, severe AEs)

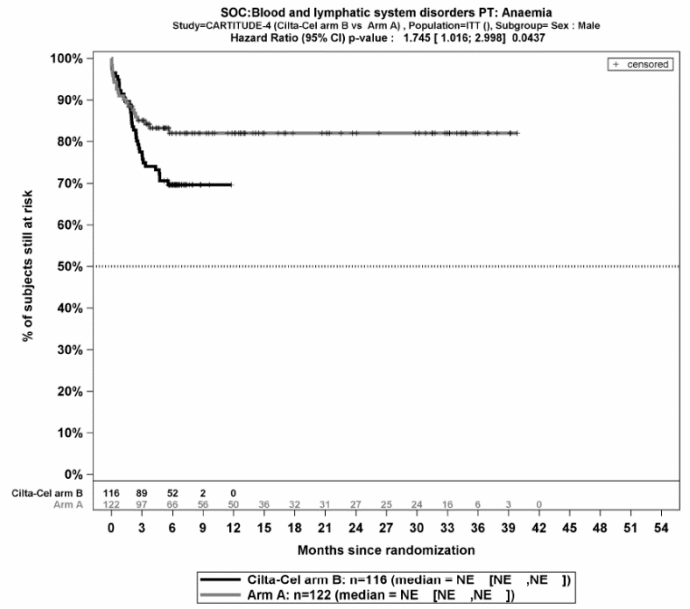

Figure 16: Kaplan-Meier curves for the outcome of anaemia (PT, severe AEs), CARTITUDE-4 study, sensitivity analysis 1, characteristic: sex, subgroup: male, data cut-off from 1 May 2024

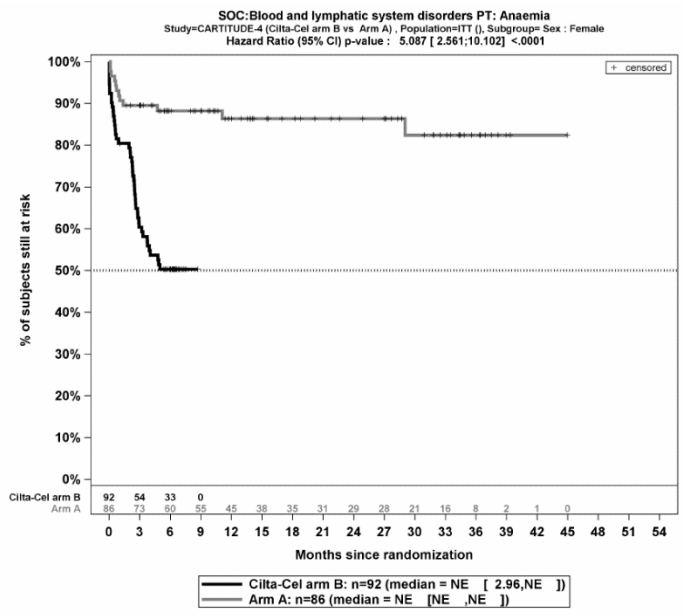

Figure 17: Kaplan-Meier curves for the outcome of anaemia (PT, severe AEs), CARTITUDE-4 study, sensitivity analysis 1, characteristic: sex, subgroup: female, data cut-off from 1 May 2024

Metabolism and nutrition disorders (SOC, severe AEs)

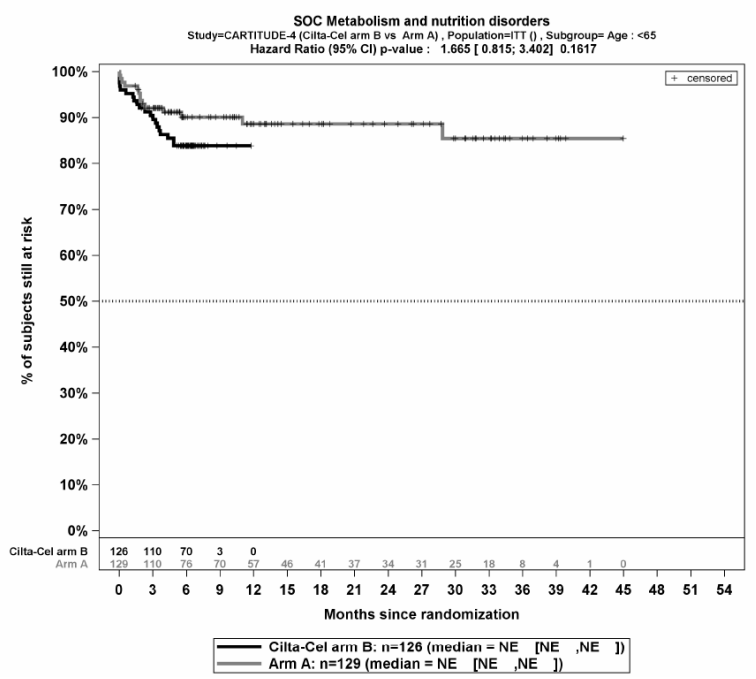

Figure 18: Kaplan-Meier curves for the outcome of anaemia (PT, severe AEs), CARTITUDE-4 study, sensitivity analysis 1, characteristic: age, subgroup: < 65 years, data cut-off from 1 May 2024

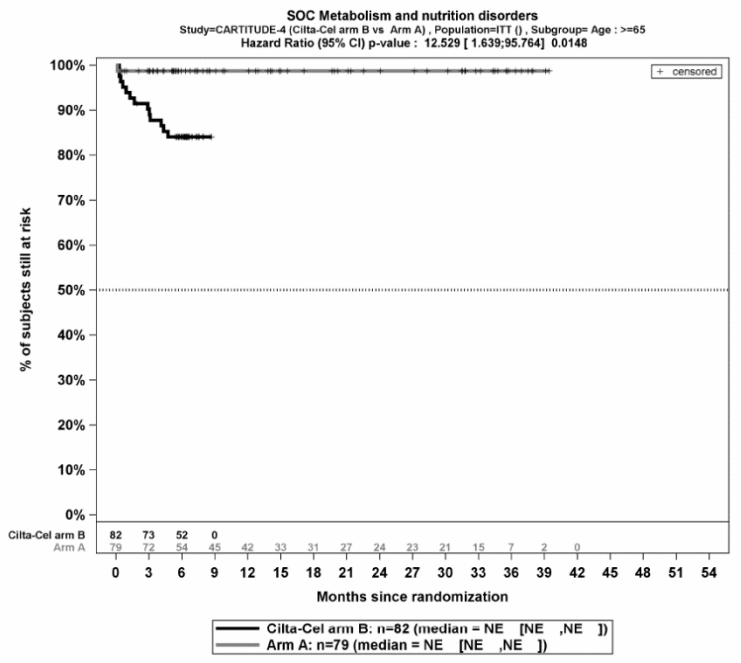

Figure 19: Kaplan-Meier curves for the outcome of anaemia (PT, severe AEs), CARTITUDE-4 study, sensitivity analysis 1, characteristic: age, subgroup: ≥ 65 years, data cut-off from 1 May 2024

Appendix B Results on side effects (sensitivity analysis 1)

Table 6: Common AEsa – RCT, direct comparison: ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd (multipage table)

Study	Patients with event n (%)	
SOC[b] PT[b]	ciltacabtagene autoleucel N = 208	individualized treatment choosing from DPd or PVd N = 208
CARTITUDE-4		
Overall AE rate	208 (100)	208 (100)
Blood and lymphatic system disorders	200 (96.2)	185 (88.9)
Neutropenia	191 (91.8)	178 (85.6)
Anaemia	117 (56.3)	57 (27.4)
Thrombocytopenia	114 (54.8)	67 (32.2)
Lymphopenia	48 (23.1)	29 (13.9)
Leukopenia	27 (13.0)	16 (7.7)
Febrile neutropenia	14 (6.7)	9 (4.3)
Immune system disorders	170 (81.7)	22 (10.6)
Cytokine release syndrome	151 (72.6)	1 (0.5)
Hypogammaglobulinaemia	75 (36.1)	18 (8.7)
Gastrointestinal disorders	162 (77.9)	121 (58.2)
Nausea	106 (51.0)	44 (21.2)
Diarrhoea	75 (36.1)	65 (31.3)
Constipation	57 (27.4)	47 (22.6)
Vomiting	30 (14.4)	18 (8.7)
Abdominal pain	10 (4.8)	17 (8.2)
Dyspepsia	10 (4.8)	6 (2.9)
General disorders and administration site conditions	145 (69.7)	147 (70.7)
Fatigue	62 (29.8)	70 (33.7)
Asthenia	37 (17.8)	34 (16.3)
Pyrexia	37 (17.8)	33 (15.9)
Oedema peripheral	36 (17.3)	28 (13.5)
Chills	14 (6.7)	9 (4.3)
Non-cardiac chest pain	11 (5.3)	7 (3.4)
Influenza like illness	2 (1.0)	10 (4.8)
Nervous system disorders	129 (62.0)	109 (52.4)
Headache	58 (27.9)	27 (13.0)
Peripheral sensory neuropathy	33 (15.9)	42 (20.2)
Dizziness	24 (11.5)	30 (14.4)
Immune effector cell-associated neurotoxicity syndrome	15 (7.2)	0 (0)

Table 6: Common AEsa – RCT, direct comparison: ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**ciltacabtagene autoleucel** **N = 208**	**individualized treatment choosing from DPd or PVd** **N = 208**
Tremor	15 (7.2)	22 (10.6)
Facial paralysis	12 (5.8)	1 (0.5)
Paraesthesia	11 (5.3)	10 (4.8)
Infections and infestations	126 (60.6)	158 (76.0)
COVID-19	17 (8.2)	63 (30.3)
Upper respiratory tract infection	15 (7.2)	52 (25.0)
Respiratory tract infection	13 (6.3)	17 (8.2)
Nasopharyngitis	12 (5.8)	21 (10.1)
COVID-19 pneumonia	11 (5.3)	14 (6.7)
Pneumonia	11 (5.3)	24 (11.5)
Urinary tract infection	11 (5.3)	15 (7.2)
Bronchitis	5 (2.4)	21 (10.1)
Metabolism and nutrition disorders	113 (54.3)	71 (34.1)
Hypokalaemia	48 (23.1)	19 (9.1)
Decreased appetite	36 (17.3)	13 (6.3)
Hypomagnesaemia	25 (12.0)	10 (4.8)
Hypophosphataemia	24 (11.5)	9 (4.3)
Hypercalcaemia	14 (6.7)	8 (3.8)
Hypocalcaemia	14 (6.7)	3 (1.4)
Hypoalbuminaemia	11 (5.3)	3 (1.4)
Hyperglycaemia	10 (4.8)	13 (6.3)
Musculoskeletal and connective tissue disorders	110 (52.9)	129 (62.0)
Back pain	35 (16.8)	46 (22.1)
Arthralgia	34 (16.3)	35 (16.8)
Bone pain	21 (10.1)	24 (11.5)
Muscle spasms	21 (10.1)	31 (14.9)
Pain in extremity	17 (8.2)	18 (8.7)
Myalgia	14 (6.7)	11 (5.3)
Musculoskeletal chest pain	13 (6.3)	22 (10.6)
Muscular weakness	8 (3.8)	14 (6.7)
Respiratory, thoracic and mediastinal disorders	96 (46.2)	94 (45.2)
Cough	32 (15.4)	38 (18.3)
Dyspnoea	29 (13.9)	43 (20.7)
Oropharyngeal pain	12 (5.8)	8 (3.8)

Table 6: Common AEsa – RCT, direct comparison: ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**ciltacabtagene autoleucel** **N = 208**	**individualized treatment choosing from DPd or PVd** **N = 208**
Nasal congestion	9 (4.3)	11 (5.3)
Epistaxis	7 (3.4)	12 (5.8)
Productive cough	6 (2.9)	11 (5.3)
Skin and subcutaneous tissue disorders	73 (35.1)	63 (30.3)
Rash	23 (11.1)	11 (5.3)
Pruritus	20 (9.6)	11 (5.3)
Investigations	54 (26.0)	46 (22.1)
Alanine aminotransferase increased	19 (9.1)	15 (7.2)
Blood alkaline phosphatase increased	14 (6.7)	4 (1.9)
Gamma glutamyltransferase increased	14 (6.7)	3 (1.4)
Aspartate aminotransferase increased	13 (6.3)	7 (3.4)
Vascular disorders	49 (23.6)	52 (25.0)
Hypotension	18 (8.7)	2 (1.0)
Hypertension	16 (7.7)	22 (10.6)
Psychiatric disorders	48 (23.1)	83 (39.9)
Insomnia	23 (11.1)	55 (26.4)
Anxiety	9 (4.3)	13 (6.3)
Depression	3 (1.4)	10 (4.8)
Injury, poisoning and procedural complications	34 (16.3)	38 (18.3)
Fall	10 (4.8)	12 (5.8)
Cardiac disorders	24 (11.5)	26 (12.5)
Eye disorders	23 (11.1)	45 (21.6)
Vision blurred	5 (2.4)	12 (5.8)
Cataract	0 (0)	15 (7.2)
Renal and urinary disorders	23 (11.1)	21 (10.1)
Reproductive system and breast disorders	11 (5.3)	12 (5.8)
Ear and labyrinth disorders	9 (4.3)	12 (5.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6 (2.9)	26 (12.5)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. Since the company did not provide any information, it is assumed that the MedDRA version corresponds to that from Module 4 A (Version 25.0) [4]; SOC and PT notation taken unmodified from the company's comments.

Table 6: Common AEsa – RCT, direct comparison: ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd (multipage table)

Study	Patients with event n (%)	
SOC[b] PT[b]	ciltacabtagene autoleucel N = 208	individualized treatment choosing from DPd or PVd N = 208

AE: adverse event; COVID-19: Coronavirus Disease 2019; DPd: daratumumab in combination with pomalidomide and dexamethasone; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PVd: pomalidomide in combination with bortezomib and dexamethasone; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 7: Common SAEsa – RCT, direct comparison: ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd

Study	Patients with event n (%)	
SOC[b] PT[b]	ciltacabtagene autoleucel N = 208	individualized treatment choosing from DPd or PVd N = 208
CARTITUDE-4		
Overall SAE rate	139 (66.8)	99 (47.6)
Infections and infestations	84 (40.4)	63 (30.3)
COVID-19 pneumonia	19 (9.1)	12 (5.8)
Pneumonia	17 (8.2)	14 (6.7)
COVID-19	11 (5.3)	7 (3.4)
Nervous system disorders	26 (12.5)	6 (2.9)
Blood and lymphatic system disorders	22 (10.6)	10 (4.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	18 (8.7)	9 (4.3)
General disorders and administration site conditions	17 (8.2)	7 (3.4)
Immune system disorders	14 (6.7)	1 (0.5)
Cytokine release syndrome	14 (6.7)	1 (0.5)
Gastrointestinal disorders	12 (5.8)	3 (1.4)
Metabolism and nutrition disorders	12 (5.8)	4 (1.9)
Musculoskeletal and connective tissue disorders	11 (5.3)	3 (1.4)
Cardiac disorders	10 (4.8)	8 (3.8)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. Since the company did not provide any information, it is assumed that the MedDRA version corresponds to that from Module 4 A (Version 25.0) [4]; SOC and PT notation taken unmodified from the company's comments.

COVID-19: Coronavirus Disease 2019; DPd: daratumumab in combination with pomalidomide and dexamethasone; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PVd: pomalidomide in combination with bortezomib and dexamethasone; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 8: Common severe AEs (CTCAE grade ≥ 3)a – RCT, direct comparison: ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd

Study	Patients with event n (%)	
SOC[b] PT[b]	ciltacabtagene autoleucel N = 208	individualized treatment choosing from DPd or PVd N = 208
CARTITUDE-4		
Overall rate of severe AEs (CTCAE grade ≥ 3)	203 (97.6)	202 (97.1)
Blood and lymphatic system disorders	199 (95.7)	180 (86.5)
Neutropenia	191 (91.8)	171 (82.2)
Thrombocytopenia	89 (42.8)	41 (19.7)
Anaemia	80 (38.5)	33 (15.9)
Lymphopenia	46 (22.1)	25 (12.0)
Leukopenia	27 (13.0)	10 (4.8)
Febrile neutropenia	14 (6.7)	9 (4.3)
Infections and infestations	53 (25.5)	62 (29.8)
COVID-19 pneumonia	9 (4.3)	14 (6.7)
Pneumonia	8 (3.8)	12 (5.8)
Metabolism and nutrition disorders	33 (15.9)	15 (7.2)
Hypokalaemia	10 (4.8)	4 (1.9)
Immune system disorders	21 (10.1)	2 (1.0)
Hypogammaglobulinaemia	12 (5.8)	2 (1.0)
Gastrointestinal disorders	15 (7.2)	14 (6.7)
Investigations	15 (7.2)	11 (5.3)
Musculoskeletal and connective tissue disorders	14 (6.7)	13 (6.3)
Nervous system disorders	14 (6.7)	13 (6.3)
Vascular disorders	11 (5.3)	10 (4.8)
General disorders and administration site conditions	10 (4.8)	15 (7.2)
Respiratory, thoracic and mediastinal disorders	10 (4.8)	12 (5.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (1.4)	10 (4.8)
Psychiatric disorders	3 (1.4)	13 (6.3)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. Since the company did not provide any information, it is assumed that the MedDRA version corresponds to that from Module 4 A (Version 25.0) [4]; SOC and PT notation taken unmodified from the company's comments.

AE: adverse event; COVID-19: Coronavirus Disease 2019; CTCAE: Common Terminology Criteria for Adverse Events; DPd: daratumumab in combination with pomalidomide and dexamethasone; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PVd: pomalidomide in combination with bortezomib and dexamethasone; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Appendix C Supplementary presentation on outcomes in the side effects category (sensitivity analysis 2)

C.1 Results

Table 9: Results (side effects, supplementary presentation, sensitivity analysis 2 with censoring as of the administration of subsequent therapies) – RCT, direct comparison: ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd (multipage table)

Study outcome category outcome	Ciltacabtagene autoleucel		Individualized treatment choosing from DPd or PVd		Ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95 %-CI] patients with event n (%)	HR [95 % CI]; p-value[a]
CARTITUDE-4					
Side effects					
AEs (supplementary information)	208	0.20 [0.13; 0.26] 208 (100)	208	0.13 [0.07; 0.20] 208 (100)	–
SAEs	208	10.28 [5.78; 15.84] 135 (64.9)	208	19.48 [12.42; 25.23] 99 (47.6)	1.26 [0.96; 1.64]; 0.097
Severe AEs[b]	208	0.72 [0.56; 0.76] 203 (97.6)	208	0.69 [0.49; 0.72] 202 (97.1)	0.93 [0.75; 1.14]; 0.455
Cytokine release syndrome	208	No suitable datac			
Severe neurological toxicity[d]	208	NA 26 (12.5)	208	NA 6 (2.9)	3.47 [1.42; 8.51]; 0.007
Infusion related reactions	No suitable data[c]				
Severe infections[e]	208	NA [29.57; NC] 82 (39.4)	208	NA [24.81; NC] 63 (30.3)	0.97 [0.69; 1.36]; 0.861
Secondary malignancies	No suitable data[c]				
Other specific AEs					
Headache (PT, AEs)	208	NA 58 (27.9)	208	NA 27 (13.0)	3.11 [1.88; 5.14]; < 0.001
Insomnia (PT, AEs)	208	NA 23 (11.1)	208	NA 55 (26.4)	0.43 [0.26; 0.71]; < 0.001

Table 9: Results (side effects, supplementary presentation, sensitivity analysis 2 with censoring as of the administration of subsequent therapies) – RCT, direct comparison: ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd (multipage table)

Study outcome category outcome	Ciltacabtagene autoleucel		Individualized treatment choosing from DPd or PVd		Ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95 %-CI] patients with event n (%)	HR [95 % CI]; p-value[a]
Thrombocytopenia (PT, severe AEs[b])	208	NA [5.95; NC] 88 (42.3)	208	NA 41 (19.7)	2.46 [1.68; 3.61]; < 0.001
Anaemia (PT, severe AEs[b])	208	NA 78 (37.5)	208	NA 33 (15.9)	2.82 [1.86; 4.28]; < 0.001
Lymphopenia (PT, severe AEs[b])	208	NA 46 (22.1)	208	NA 25 (12.0)	2.04 [1.23; 3.36]; 0.005
Leukopenia (PT, severe AEs[b])	208	NA 27 (13.0)	208	NA 10 (4.8)	2.76 [1.34; 5.71]; 0.006
Metabolism and nutrition disorders (SOC, severe AEs[b])	208	NA 33 (15.9)	208	NA 15 (7.2)	2.48 [1.30; 4.71]; 0.006
Hypogammaglobulinaemia (PT, severe AEs[b])	208	NA [8.02; NC] 12 (5.8)	208	NA 2 (1.0)	52.97 [5.43; 516.74]; < 0.001

a. Since the company did not provide any information, it is assumed that the analysis methods correspond to those from Module 4 A [4]: HR, CI and p-value: Cox proportional hazards model, stratified by comparator therapy of investigator's choice (DPd vs. PVd), ISS stage (I vs. II vs. III) and number of prior lines of therapy (1 vs. 2 or 3).
b. Operationalized as CTCAE grade ≥ 3.
c. See Section 2.1.2.3 for reasons.
d. Operationalized as SAEs of the SOC “nervous system disorders”.
e. Operationalized as SAEs of the SOC “infections and infestations”.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; DPd: daratumumab in combination with pomalidomide and dexamethasone; HR: hazard ratio; ISS: International Staging System; n: number of patients with (at least 1) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; PVd: pomalidomide in combination with bortezomib and dexamethasone; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

C.2 Kaplan-Meier curves

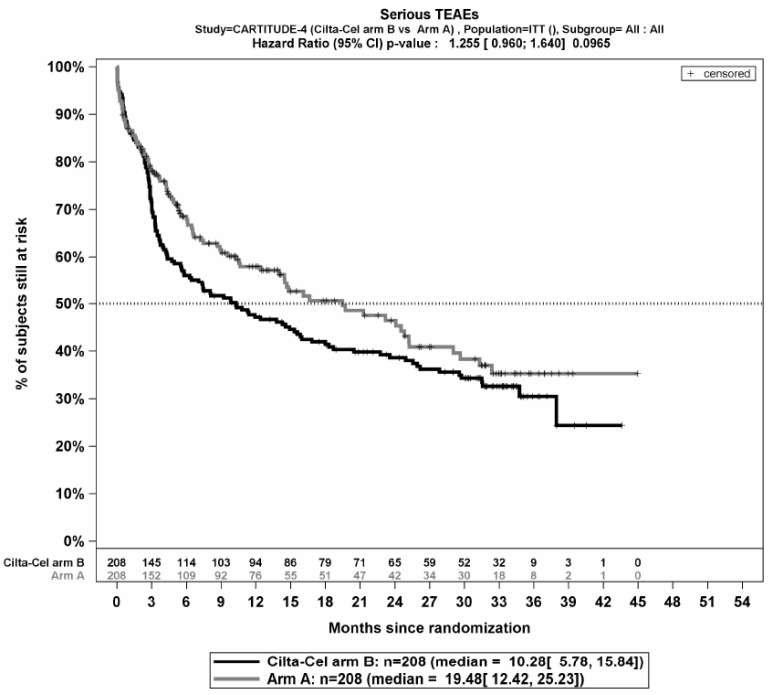

Figure 20: Kaplan-Meier curves for the outcome of SAEs, CARTITUDE-4 study, sensitivity analysis 2, data cut-off from 01 May 2024

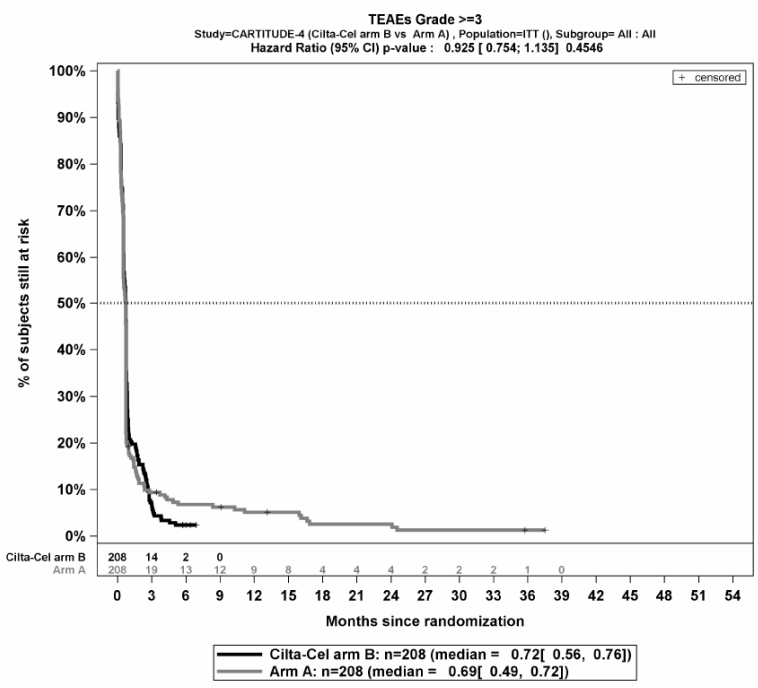

Figure 21: Kaplan-Meier curves for the outcome of severe AEs, CARTITUDE-4 study, sensitivity analysis 2, data cut-off from 1 May 2024

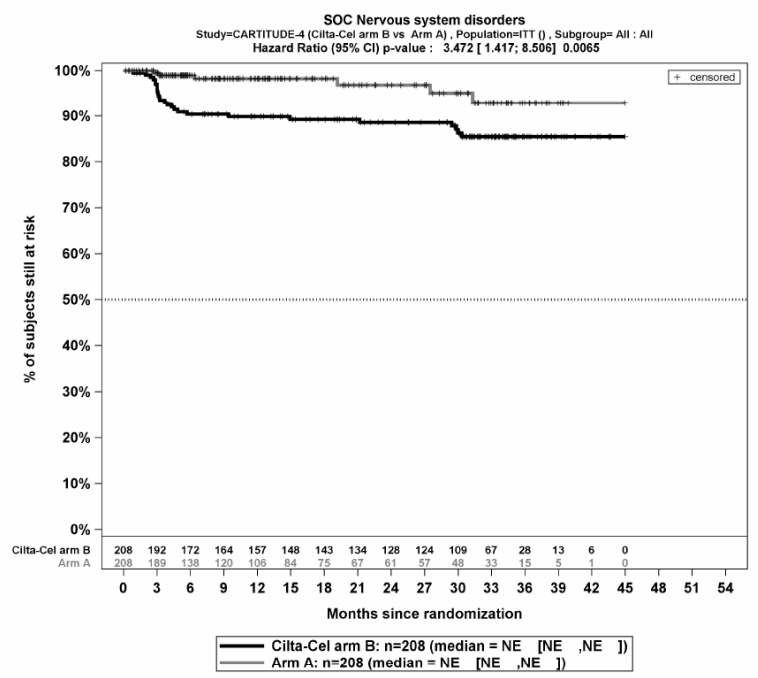

Figure 22: Kaplan-Meier curves for the outcome of severe neurological toxicity (operationalized via SAEs of the SOC “nervous system disorders”), CARTITUDE-4 study, sensitivity analysis 2, data cut-off from 01.05.2024

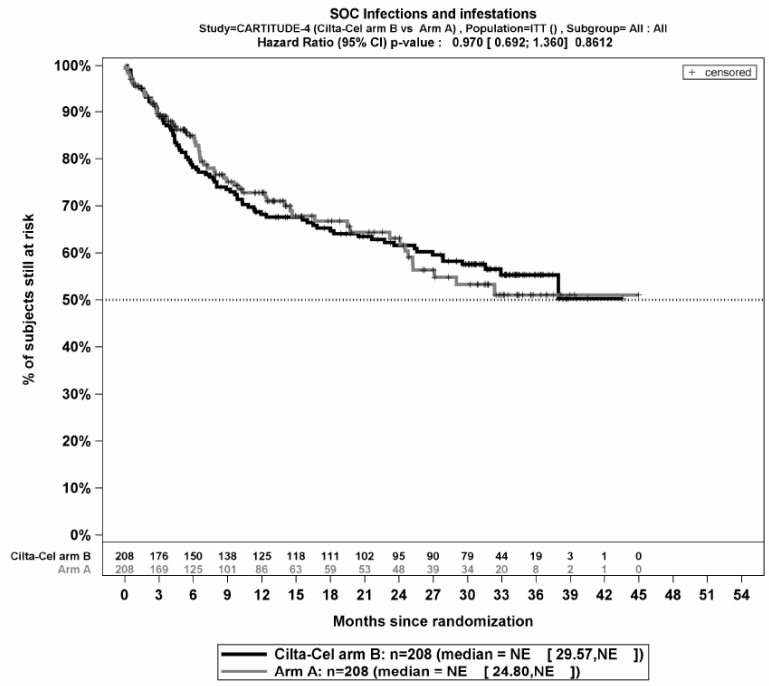

Figure 23: Kaplan-Meier curves for the outcome of severe infections (operationalized via SAEs of the SOC “infections and infestations”), CARTITUDE-4 study, sensitivity analysis 2, data cut from 1 May 2024

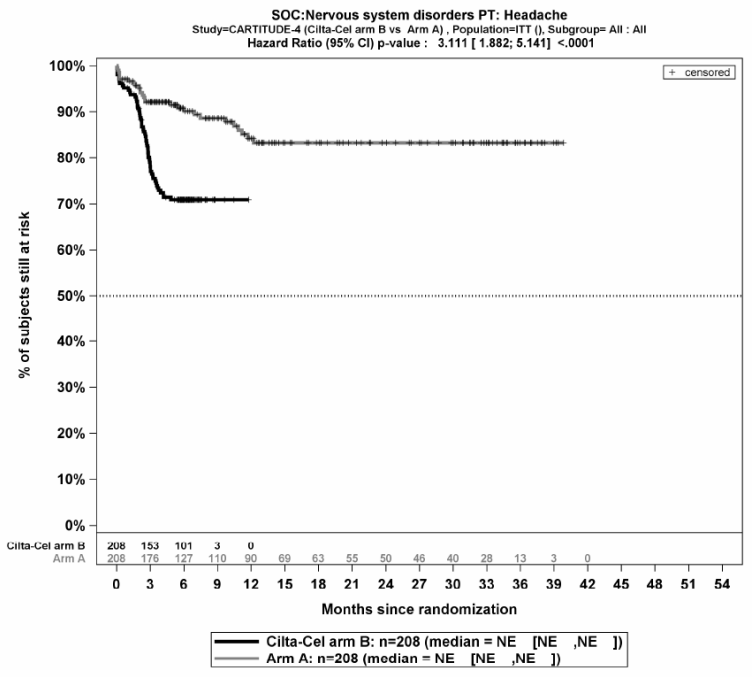

Figure 24: Kaplan-Meier curves for the outcome of headache (PT, AEs), CARTITUDE-4 study, sensitivity analysis 2, data cut-off from 1 May 2024

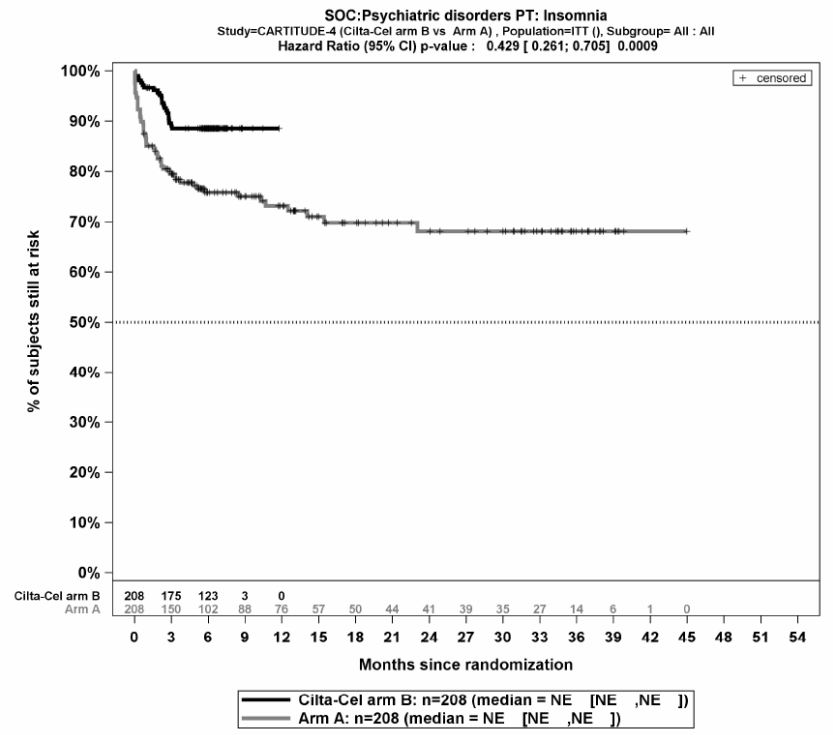

Figure 25: Kaplan-Meier curves for the outcome of insomnia (PT, AEs), CARTITUDE-4 study, sensitivity analysis 2, data cut-off from 1 May 2024

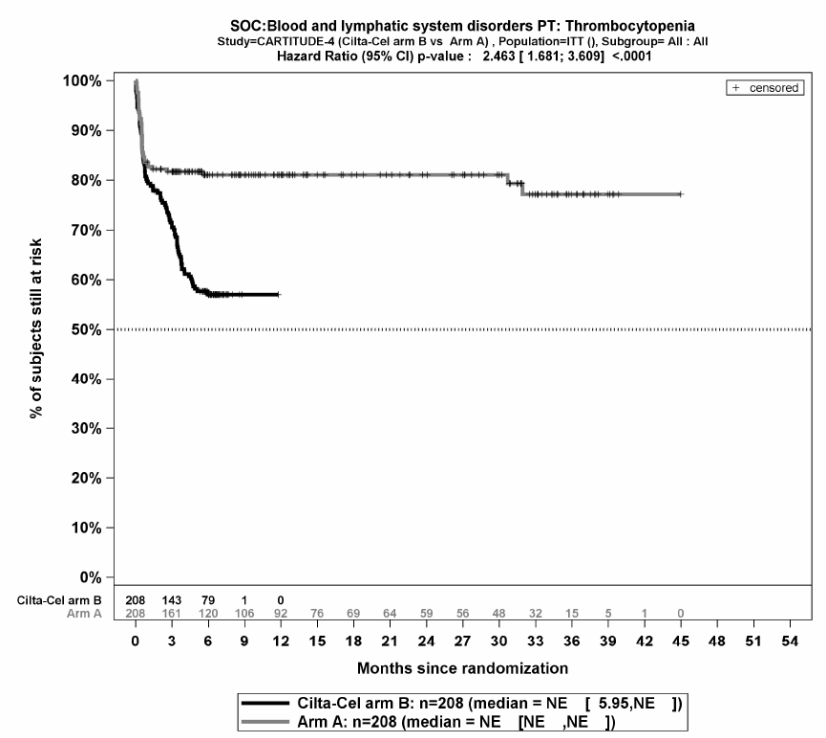

Figure 26: Kaplan-Meier curves for the outcome of thrombocytopenia (PT, severe AEs), CARTITUDE-4 study, sensitivity analysis 2, data cut-off from 1 May 2024

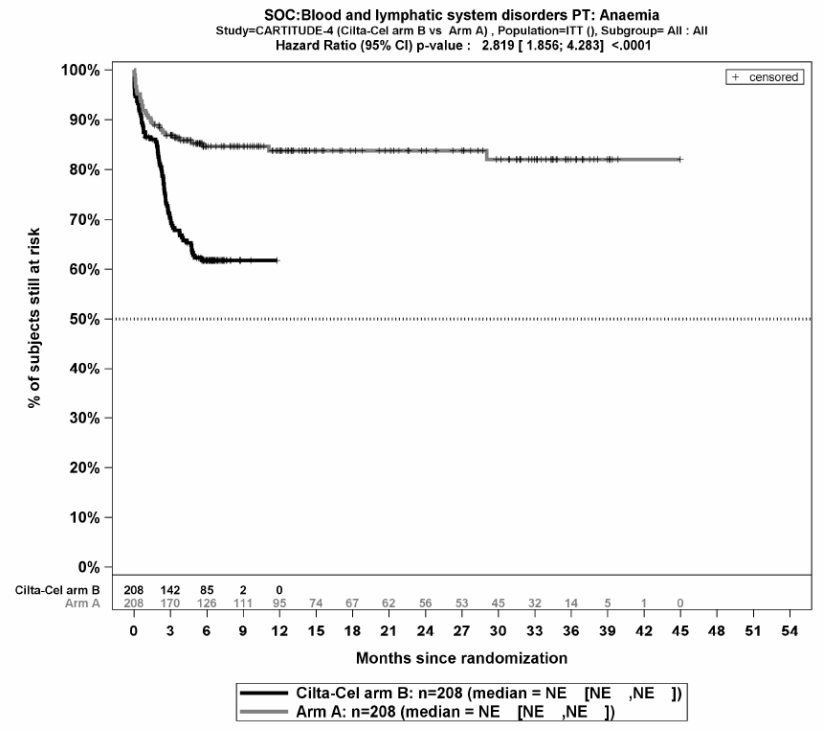

Figure 27: Kaplan-Meier curves for the outcome of anaemia (PT, severe AEs), CARTITUDE-4 study, sensitivity analysis 2, data cut-off from 1 May 2024

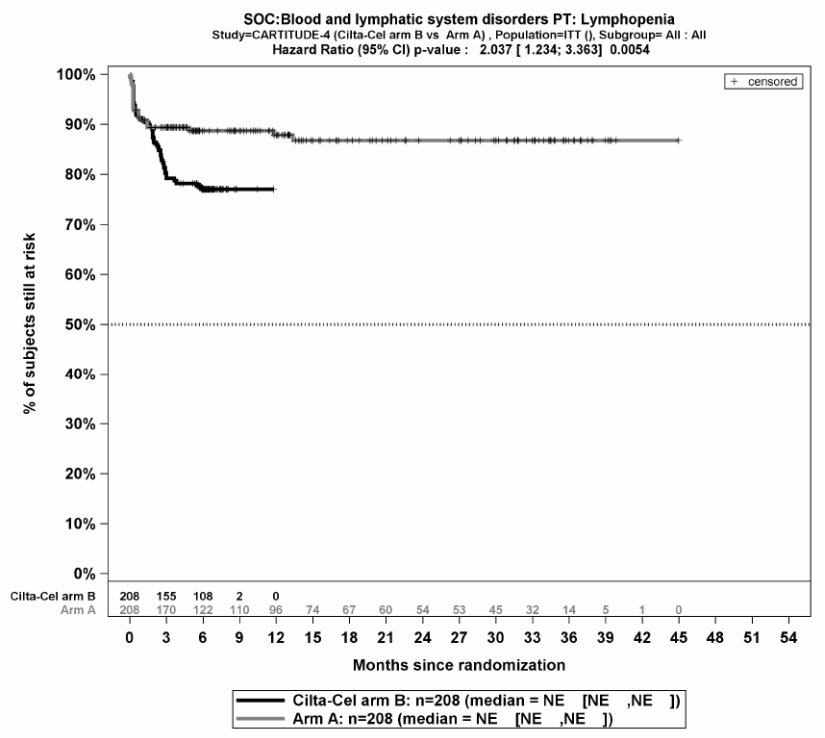

Figure 28: Kaplan-Meier curves for the outcome of lymphopenia (PT, severe AEs), CARTITUDE-4 study, sensitivity analysis 2, data cut-off from 1 May 2024

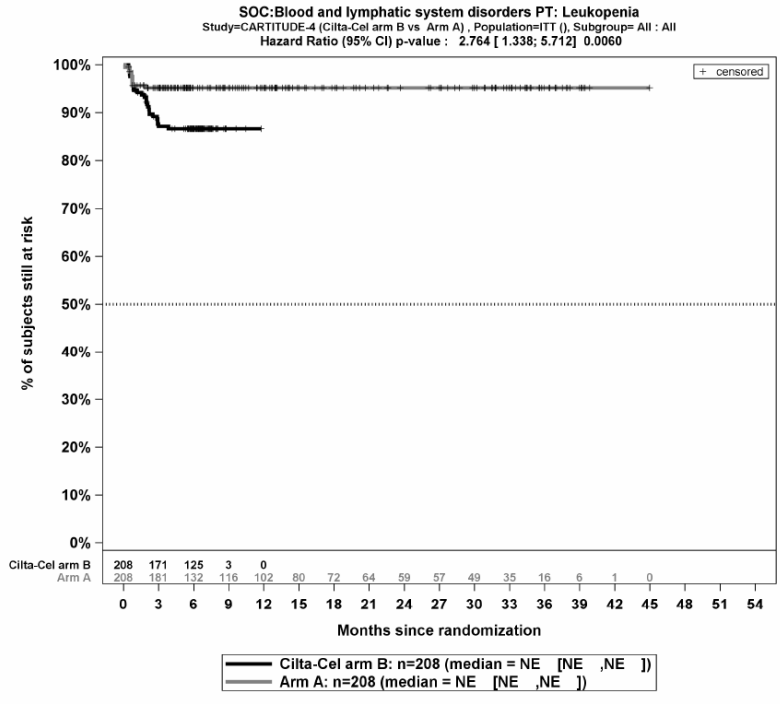

Figure 29: Kaplan-Meier curves for the outcome of leukopenia (PT, severe AEs), CARTITUDE-4 study, sensitivity analysis 2, data cut-off from 1 May 2024

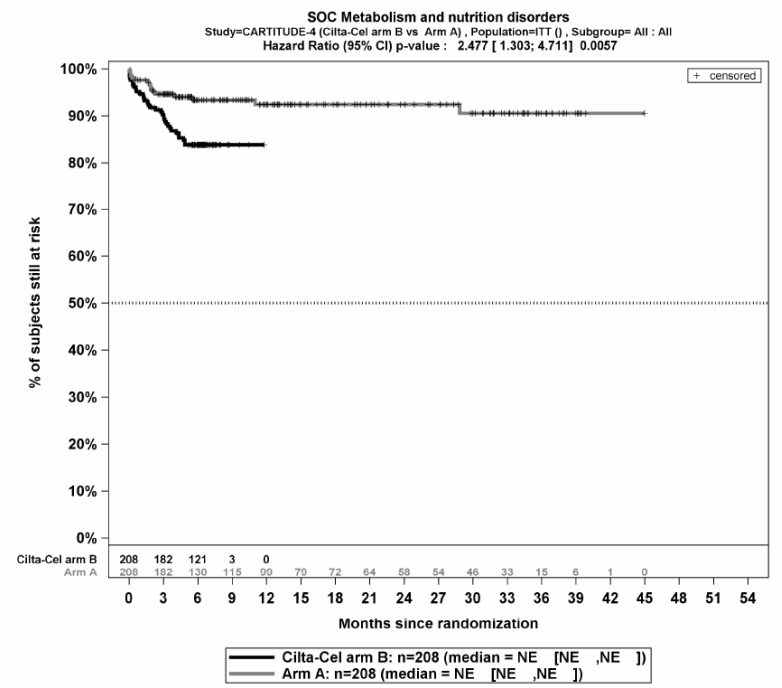

Figure 30: Kaplan-Meier curves for the outcome of metabolism and nutrition disorders (SOC, severe AEs), CARTITUDE-4 study, sensitivity analysis 2, data cut-off from 1 May 2024

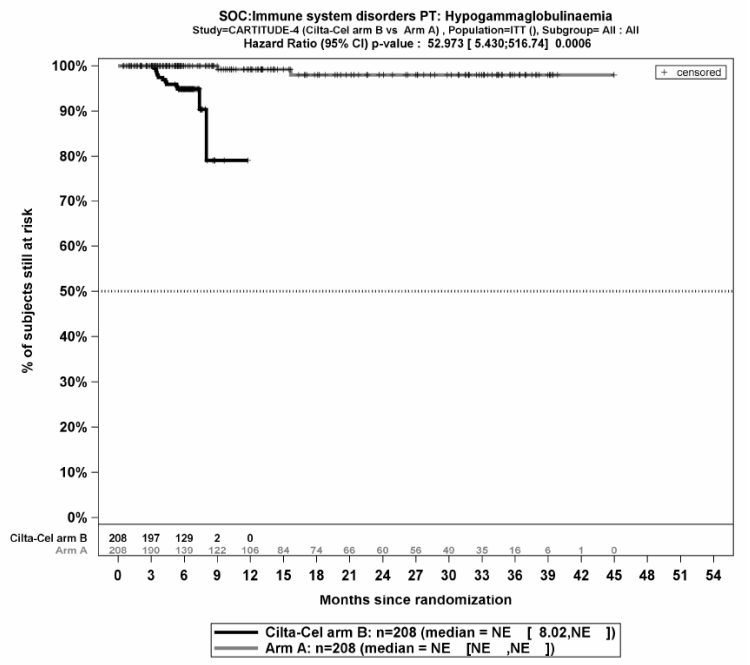

Figure 31: Kaplan-Meier curves for the outcome of hypogammaglobulinaemia (PT, severe AEs), CARTITUDE-4 study, sensitivity analysis 2, data cut-off from 1 May 2024

Appendix D Supplementary presentation of sensitivity analyses for patient-reported outcomes

D.1 Sensitivity analysis 1 (time to first deterioration)

D.1.1 Results

Table 10: Results (morbidity, health-related quality of life, time to event) – RCT, direct comparison: ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd (multipage table)

Study outcome category outcome	Ciltacabtagene autoleucel		Individualized treatment choosing from DPd or PVd		Ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd
	N[a]	median time to event in months [95% CI] patients with event n (%)	N[a]	median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value[b]
CARTITUDE-4					
Morbidity					
Symptoms (EORTC QLQ-C30 - time to first deterioration by ≥ 10 points[c])					
Fatigue	161	8.81 [4.83; NC] 95 (45.7)	162	6.08 [3.06; 9.43] 95 (45.0)	0.73 [0.54; 0.97]; 0.029
Nausea and vomiting	159	NA 59 (28.4)	163	35.65 [35.65; NC] 44 (20.9)	0.93 [0.62; 1.37]; 0.698
Pain	162	NA [23.03; NC] 72 (34.6)	164	32.20 [29.14; NC] 61 (28.9)	0.86 [0.61; 1.21]; 0.377
Dyspnoea	162	33.97 [17.38; NC] 80 (38.5)	163	16.72 [8.67; NC] 78 (37.0)	0.74 [0.54; 1.02]; 0.069
Insomnia	161	38.90 [28.06; NC] 71 (34.1)	163	18.86 [11.20; NC] 66 (31.3)	0.74 [0.53; 1.05]; 0.091
Appetite loss	159	39.92 [29.01; NC] 64 (30.8)	163	NA 47 (22.3)	1.02 [0.70; 1.49]; 0.916
Constipation	159	NA [33.97; NC] 53 (25.5)	163	18.86 [8.67; NC] 72 (34.1)	0.47 [0.33; 0.68]; < 0.001
Diarrhoea	161	34.00 [28.52; NC] 68 (32.7)	162	NA 47 (22.3)	1.05 [0.72; 1.53]; 0.816
Symptoms (PGIS - time to 1st deterioration by ≥ 1 point[d])	162	NA 39 (18.8)	164	NA 37 (17.5)	0.82 [0.52; 1.29]; 0.391

Table 10: Results (morbidity, health-related quality of life, time to event) – RCT, direct comparison: ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd (multipage table)

Study **outcome category** **outcome**	**Ciltacabtagene autoleucel**		**Individualized treatment choosing from DPd or PVd**		**Ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd**
	N[a]	**median time to event in months [95% CI]** **patients with event n (%)**	**N[a]**	**median time to event in months [95% CI]** **patients with event n (%)**	**HR [95% CI]; p-value[b]**
Symptoms (MySIm-Q Total Symptom Score - time to 1st deterioration ≥ 15 points[e])	162	NA 21 (10.1)	161	NA 26 (12.3)	0.49 [0.27; 0.89]; 0.018
Health status (EQ-5D VAS – time to first deterioration by ≥ 15 points[f])	162	NA [31.39; NC] 59 (28.4)	159	NA [34,01; NC] 36 (17.1)	1.19 [0.78; 1.82]; 0.414
Health-related quality of life					
EORTC QLQ-C30 - time to first deterioration by ≥ 10 points)[g]					
Global health status	162	NA [9.40; NC] 80 (38.5)	164	12.45 [8.54; 34.33] 78 (37.0)	0.76 [0.55; 1.04]; 0.087
Physical functioning	162	NA [29.14; NC] 63 (30.3)	163	28.39 [7.03; NC] 70 (33.2)	0.61 [0.43; 0.86]; 0.005
Role functioning	162	22.24 [7.26; NC] 88 (42.3)	164	5.98 [3.25; 11.27] 93 (44.1)	0.70 [0.52; 0.94]; 0.019
Emotional functioning	162	NA [33.38; NC] 62 (29.8)	164	34.00 [29.37; NC] 52 (24.6)	0.97 [0.67; 1.41]; 0.876
Cognitive functioning	162	24.38 [11.07; NC] 85 (40.9)	164	9.20 [5.72; 12.65] 87 (41.2)	0.68 [0.50; 0.92]; 0.012
Social functioning	161	9.17 [6.18; NC] 95 (45.7)	163	12.19 [6.31; 31.93] 83 (39.3)	0.93 [0.69; 1.26]; 0.643
MySIm-Q Total Impact Score – time to first deterioration by ≥ 15 points[e]	162	NA [34.23; NC] 45 (21.6)	161	NA 36 (17.1)	0.93 [0.60; 1.46]; 0.760

Table 10: Results (morbidity, health-related quality of life, time to event) – RCT, direct comparison: ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd (multipage table)

Study outcome category outcome	Ciltacabtagene autoleucel		Individualized treatment choosing from DPd or PVd		Ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd
	N[a]	median time to event in months [95% CI] patients with event n (%)	N[a]	median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value[b]

a. Number of patients with values at baseline and at least one value during the course of the study [3]. Only these patients can contribute data to the time-to-event analysis. Smaller number of patients than in the MMRM analyses, presumably because not all recording time points were used for the event time analyses.
b. HR, CI and p-value: Cox PH model, stratified by comparator therapy of investigator's choice (DPd vs. PVd), ISS stage (I vs. II vs. III) and number of previous lines of treatment (1 vs. 2 or 3).
c. An increase by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
d. An increase by ≥ 1 point from baseline is considered a clinically relevant deterioration (scale range from "normal, not at all ill" to "severely ill"; in Module 4 A, the company converted the scale for the analyses into numerical values from 1 ["normal, not at all ill"] to 5 ["severely ill"] [4]).
e. An increase by ≥ 15 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
f. A decrease by ≥ 15 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
g. A decrease by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).

CI: Confidence Interval; DPd: daratumumab in combination with pomalidomide and dexamethasone; EORTC: European Organisation for Research and Treatment of Cancer; HR: Hazard Ratio; n: Number of patients with (at least 1) event; MySIm-Q: Multiple Myeloma Symptom and Impact Questionnaire; N: Number of analysed patients; NA: not achieved; NC: not calculable; PGIS: Patient Global Impression of Severity; PVd: Pomalidomide in combination with bortezomib and dexamethasone; QLQ-C30: Quality of Life Questionnaire - Core 30; RCT: randomized controlled trial; VAS: visual analogue scale

D.1.2 Kaplan-Meier curves

Morbidity

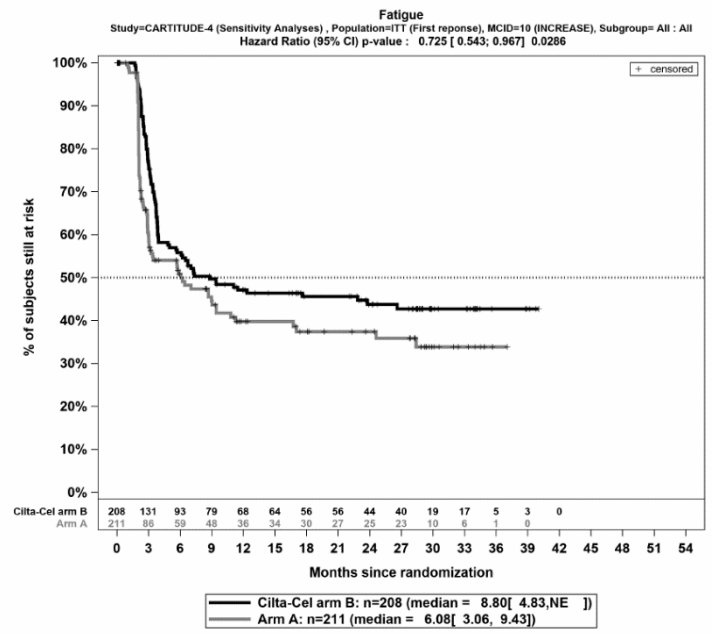

Figure 32: Kaplan-Meier curves for the time to first deterioration of the EORTC QLQ-C30 fatigue symptom scale (response threshold 10 points), CARTITUDE-4 study, data cut-off of 1 May 2024

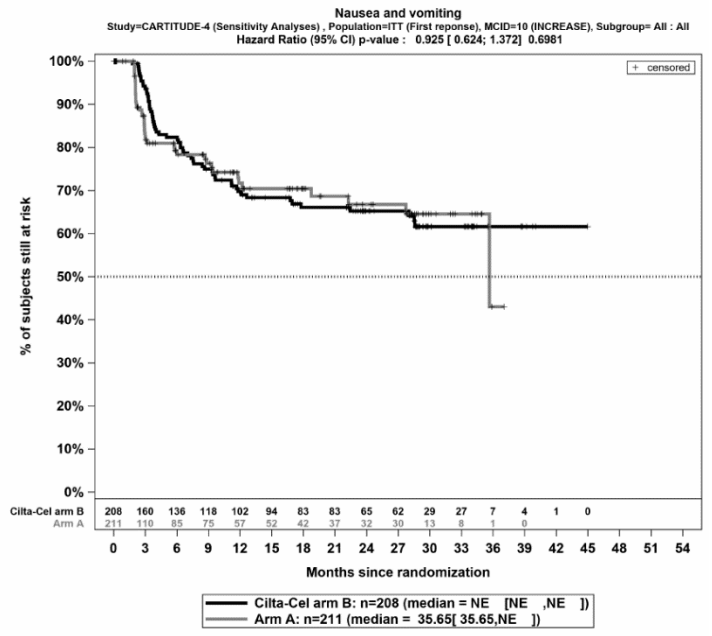

Figure 33: Kaplan-Meier curves for the time to first deterioration of the EORTC QLQ-C30 nausea and vomiting symptom scale (response threshold 10 points), CARTITUDE-4 study, data cut-off of 1 May 2024

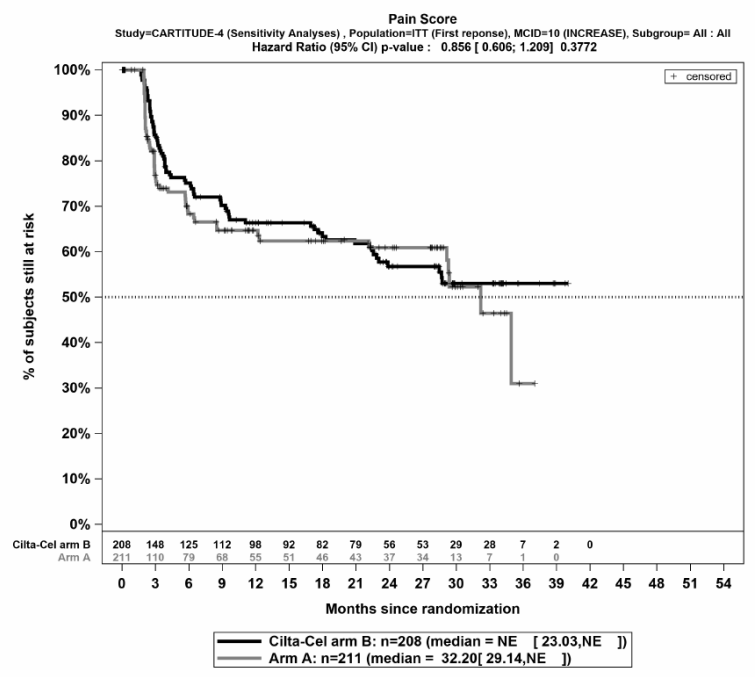

Figure 34: Kaplan-Meier curves for the time to first deterioration of the EORTC QLQ-C30 pain symptom scale (response threshold 10 points), CARTITUDE-4 study, data cut-off of 1 May 2024

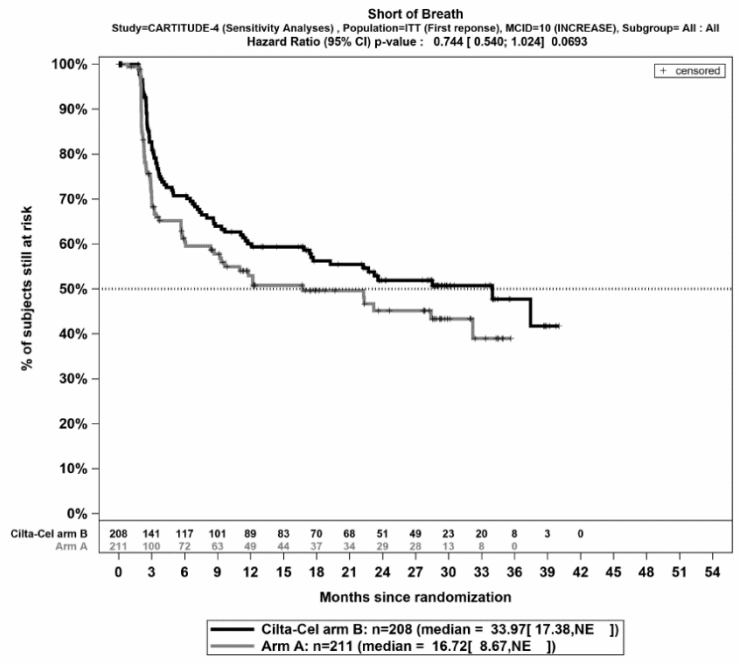

Figure 35: Kaplan-Meier curves for the time to first deterioration of the EORTC QLQ-C30 dyspnoea symptom scale (response threshold 10 points), CARTITUDE-4 study, data cut-off of 1 May 2024

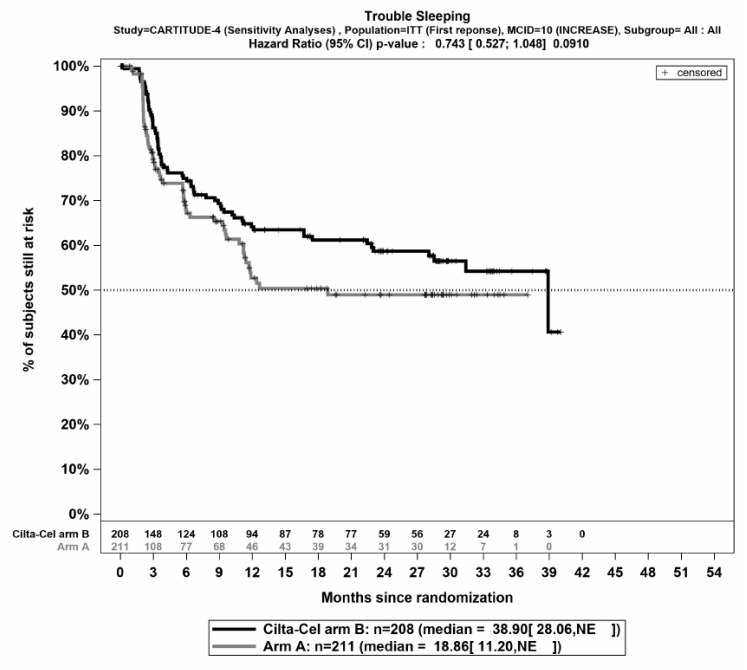

Figure 36: Kaplan-Meier curves for the time to first deterioration of the EORTC QLQ-C30 insomnia symptom scale (response threshold 10 points), CARTITUDE-4 study, data cut-off of 1 May 2024

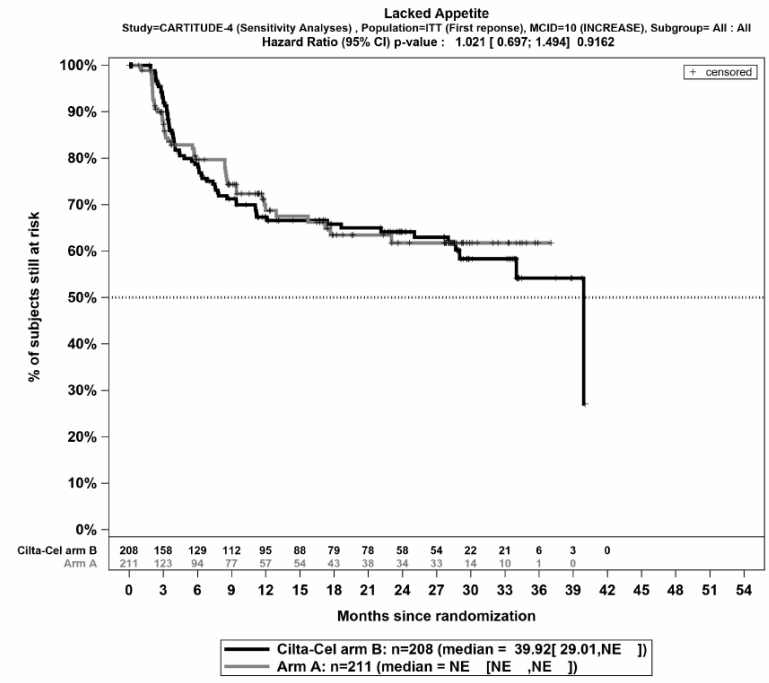

Figure 37: Kaplan-Meier curves for the time to first deterioration of the EORTC QLQ-C30 appetite loss symptom scale (response threshold 10 points), CARTITUDE-4 study, data cut-off of 1 May 2024

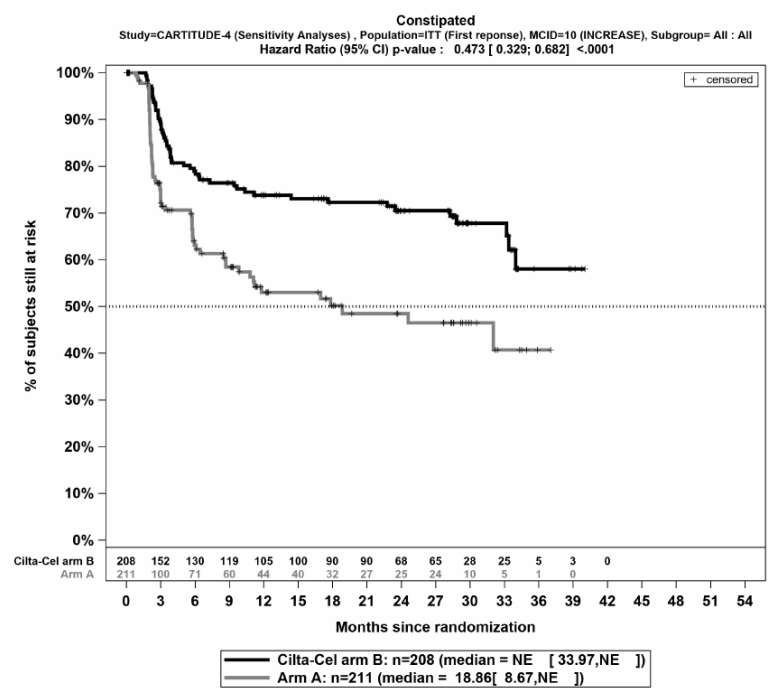

Figure 38: Kaplan-Meier curves for the time to first deterioration of the EORTC QLQ-C30 constipation symptom scale (response threshold 10 points), CARTITUDE-4 study, data cut-off of 1 May 2024

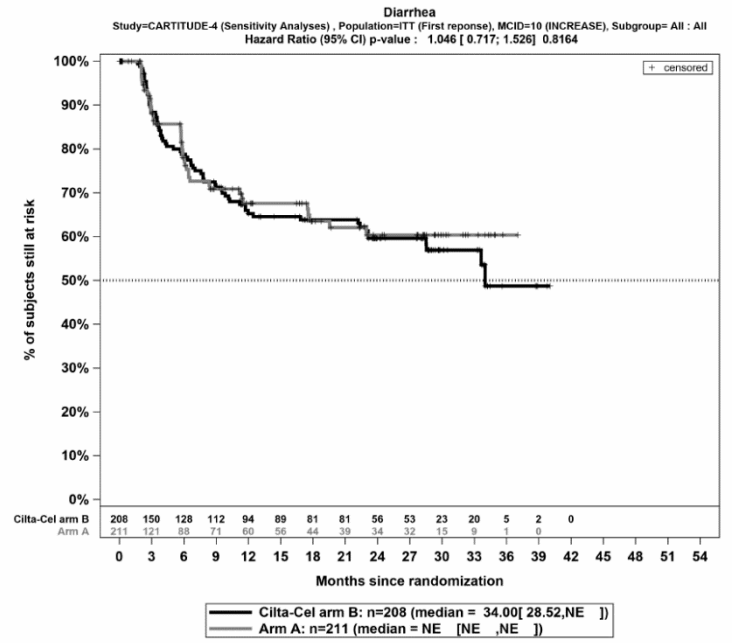

Figure 39. Kaplan-Meier curves for the time to first deterioration of the EORTC QLQ-C30 diarrhoea symptom scale (response threshold 10 points), CARTITUDE-4 study, data cut-off of 1 May 2024

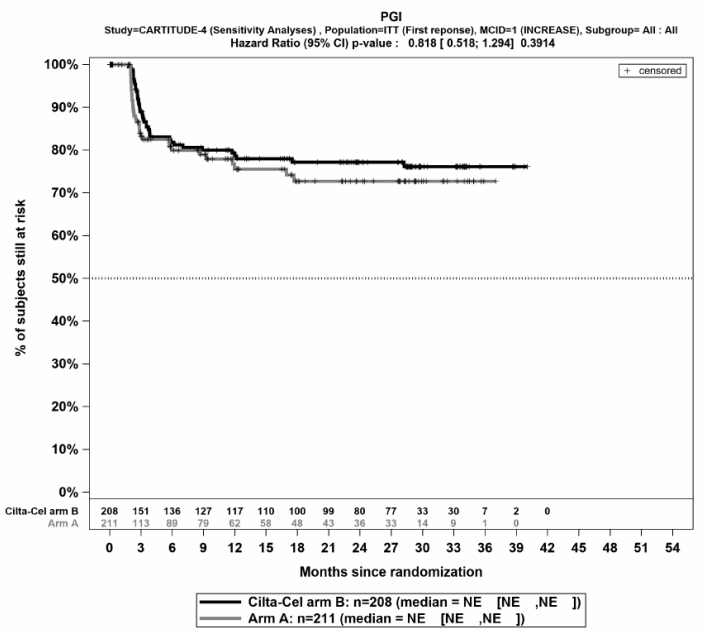

Figure 40: Kaplan-Meier curves for the time to first deterioration of the PGIS symptom scale (response threshold 1 point), CARTITUDE-4 study, data cut-off of 1 May 2024

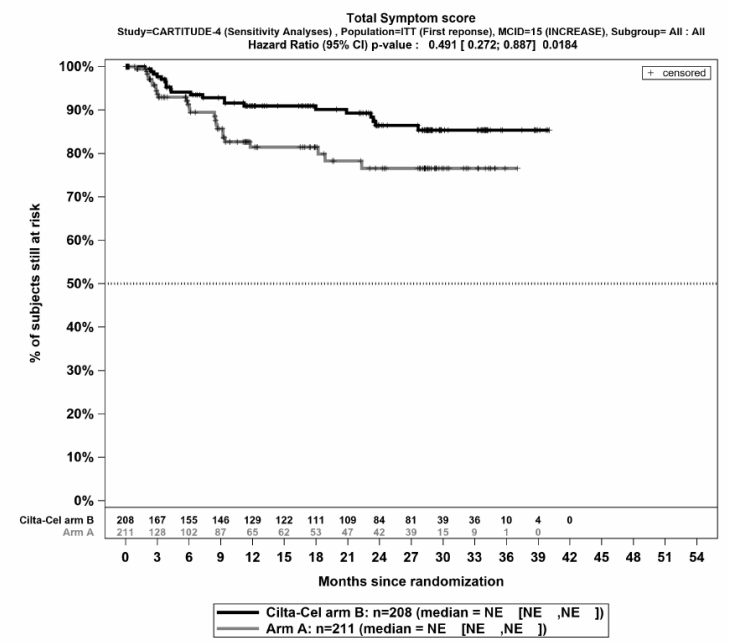

Figure 41: Kaplan-Meier curves for the time to first deterioration of the MySIm-Q symptom scale (Total Symptom Score; response threshold 15 points), CARTITUDE-4 study, data cut-off of 1 May 2024

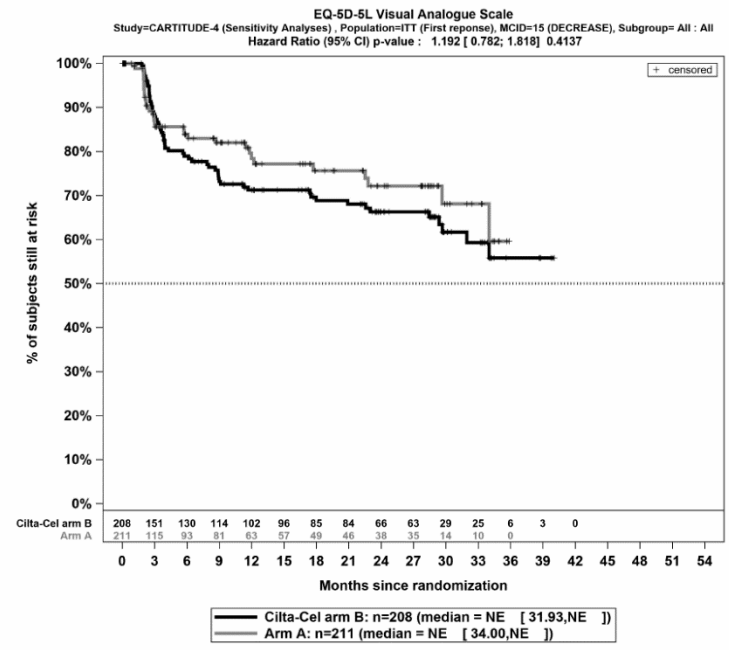

Figure 42: Kaplan-Meier curves for the time to first deterioration of the health status symptom scale (EQ-5D VAS; response threshold 15 points), CARTITUDE-4 study, data cut-off of 1 May 2024

Health-related quality of life

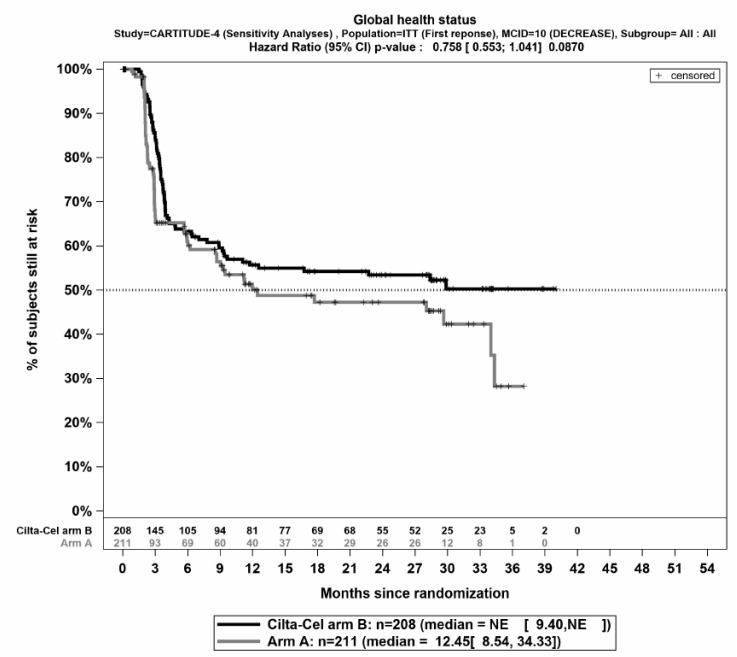

Figure 43: Kaplan-Meier curves for the time to first deterioration of the outcome of global health status of the EORTC QLQ-C30 (response threshold 10 points), CARTITUDE-4 study, data cut-off of 1 May 2024

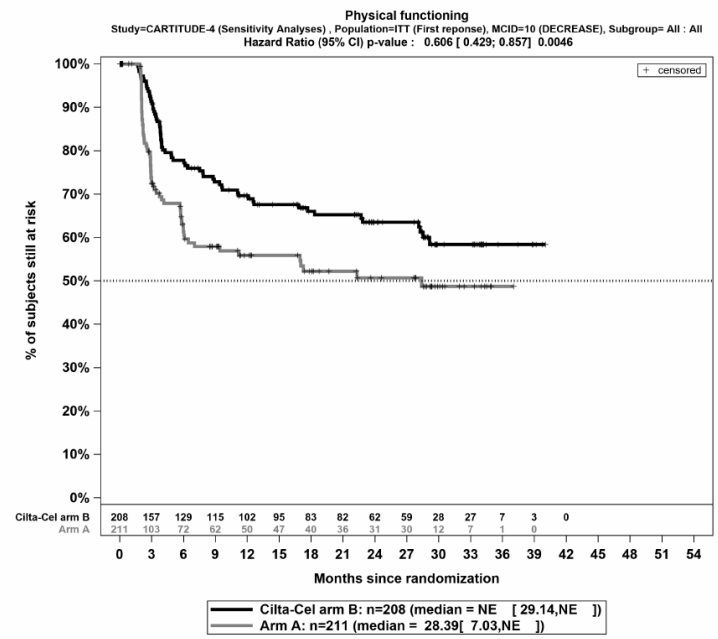

Figure 44: Kaplan-Meier curves for the time to first deterioration of the outcome of physical functioning of the EORTC QLQ-C30 (response threshold 10 points), CARTITUDE-4 study, data cut-off of 1 May 2024

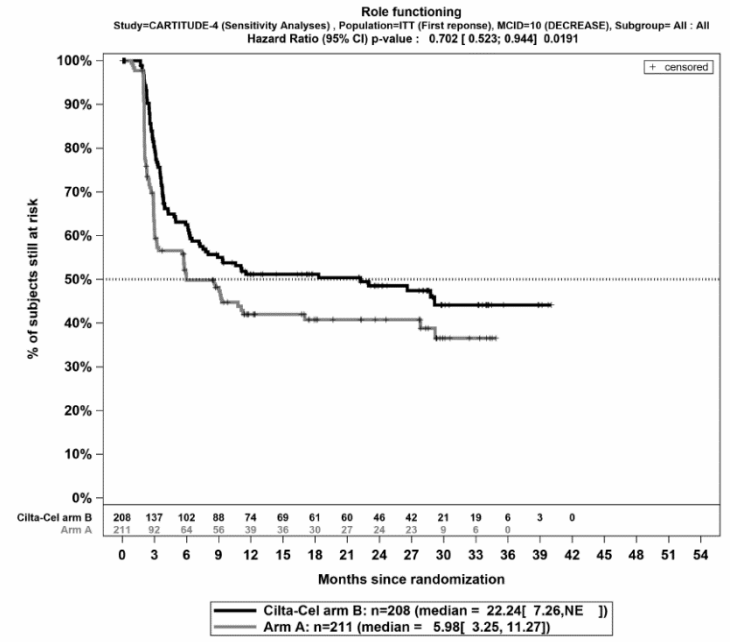

Figure 45: Kaplan-Meier curves for the time to first deterioration of the outcome of role functioning of the EORTC QLQ-C30 (response threshold 10 points), CARTITUDE-4 study, data cut-off of 1 May 2024

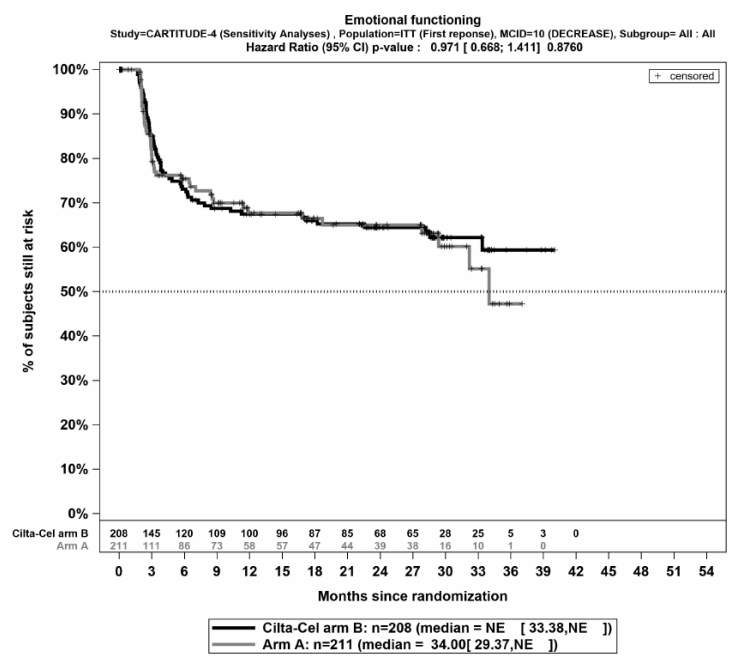

Figure 46: Kaplan-Meier curves for the time to first deterioration of the outcome of emotional functioning of the EORTC QLQ-C30 (response threshold 10 points), CARTITUDE-4 study, data cut-off of 1 May 2024

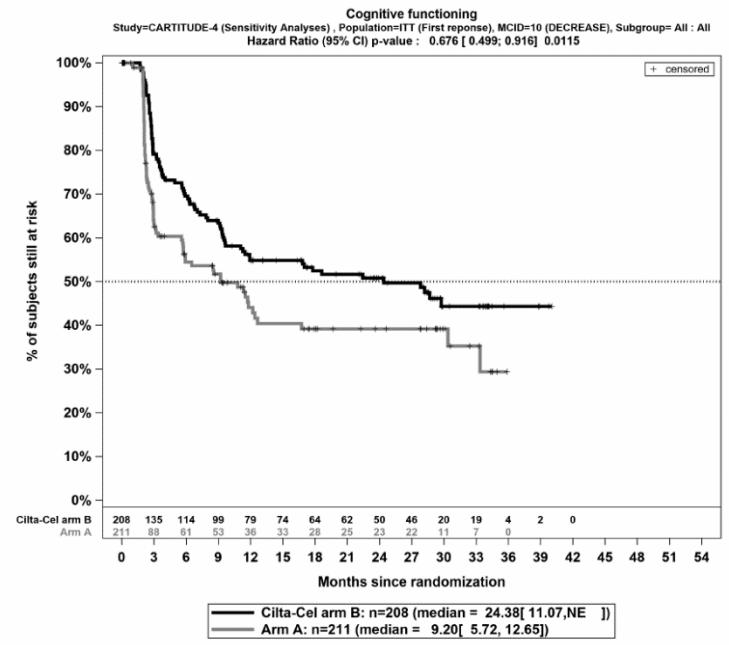

Figure 47: Kaplan-Meier curves for the time to first deterioration of the outcome of cognitive functioning of the EORTC QLQ-C30 (response threshold 10 points), CARTITUDE-4 study, data cut-off of 1 May 2024

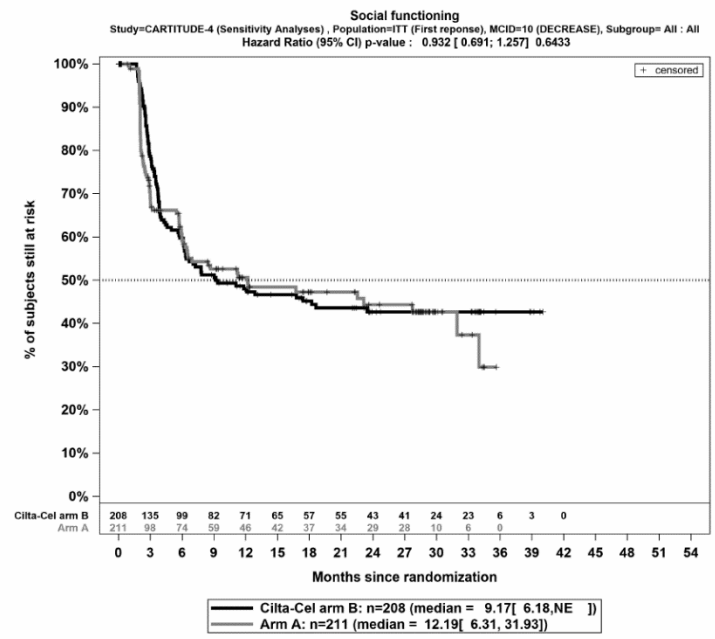

Figure 48: Kaplan-Meier curves for the time to first deterioration of the outcome of social functioning of the EORTC QLQ-C30 (response threshold 10 points), CARTITUDE-4 study, data cut-off of 1 May 2024

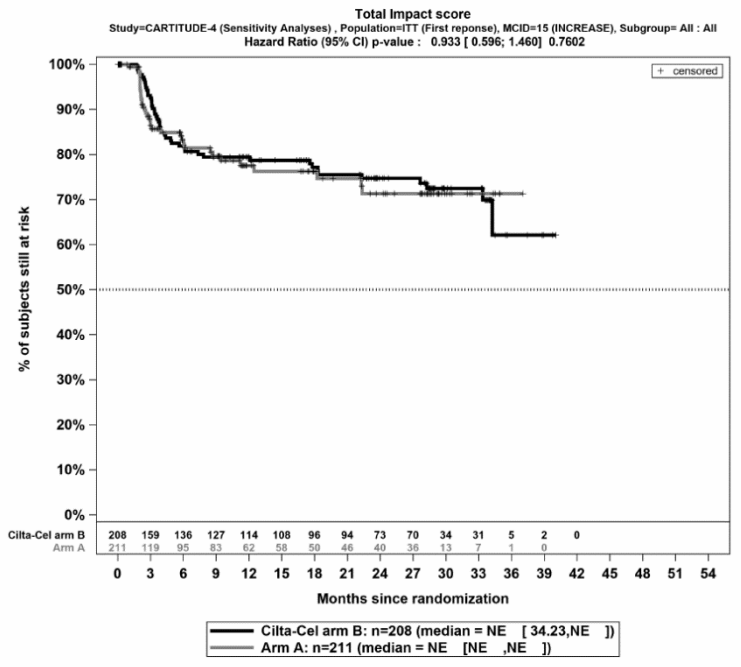

Figure 49: Kaplan-Meier curves for the time to first deterioration of the outcome of MySIm-Q (Total Impact Score; response threshold 15 points), CARTITUDE-4 study, data cut-off of 1 May 2024

D.2 Sensitivity analysis 2 (continuous analysis using MMRM)

Table 11: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd (multipage table)

Study outcome category outcome	Ciltacabtagene autoleucel			Individualized treatment choosing from DPd or PVd			Ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd
	N[a]	values at baseline mean (SD)	mean change in the course of the study mean[b] (SE)	N[a]	values at baseline mean (SD)	mean change in the course of the study mean[b] (SE)	MD [95% CI]; p-value[b]
CARTITUDE-4							
Morbidity							
Symptoms (EORTC QLQ-C30[c])							
Fatigue	184	37.3 (26.2)	-7.1 (2.1)	176	35.9 (24.3)	-2.7 (2.0)	-4.36 [-7.41; -1.30]; 0.005 SMD [95% CI] -0.29 [-0.50; -0.09][d]
Nausea and vomiting	182	6.3 (13.6)	-1.2 (1.0)	178	4.1 (9.8)	-0.9 (1.0)	-0.35 [-1.86; 1.16]; 0.651
Pain	185	37.2 (29.9)	-9.4 (2.0)	178	30.7 (27.8)	-6.6 (2.0)	-2.83 [-6.16; 0.50]; 0.096
Dyspnoea	185	19.0 (22.5)	-3.0 (2.1)	177	19.0 (21.8)	5.7 (2.1)	–8.71 [–12.2; –5.24]; < 0.001 SMD [95% CI] -0.51 [-0.72; -0.31][d]
Insomnia	184	31.1 (32.0)	-5.3 (2.4)	177	28.8 (28.0)	0.0 (2.4)	-5.36 [-9.14; -1.58]; 0.006 SMD [95% CI] -0.29 [-0.50; -0.08][d]
Appetite loss	182	14.9 (25.6)	-0.1 (1.8)	178	12.5 (21.8)	-1.7 (1.8)	1.64 [-1.14; 4.41]; 0.248
Constipation	182	14.5 (25.1)	-3.6 (2.1)	178	13.8 (22.5)	5.6 (2.1)	–9.21 [–12.8; –5.65]; < 0.001 SMD [95% CI] -0.53 [-0.74; -0.32][d]
Diarrhoea	184	18.6 (26.9)	-3.0 (2.1)	177	17.5 (24.0)	-4.9 (2.1)	1.88 [-1.34; 5.10]; 0.251
Symptoms (PGIS[e])	185	3.2 (0.9)	-0.9 (0.1)	178	3.1 (0.9)	-0.5 (0.1)	–0.44 [–0.57; –0.31]; < 0.001 SMD [95% CI] -0.68 [-0.89; -0.47][d]

Table 11: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd (multipage table)

Study outcome category outcome	Ciltacabtagene autoleucel			Individualized treatment choosing from DPd or PVd			Ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd
	N[a]	values at baseline mean (SD)	mean change in the course of the study mean[b] (SE)	N[a]	values at baseline mean (SD)	mean change in the course of the study mean[b] (SE)	MD [95% CI]; p-value[b]
Symptoms (MySIm-Q Total Symptom Score[c])	185	1.1 (0.69)	-0.2 (0.1)	174	1.0 (0.6)	0.0 (0.1)	-0.18 (-0.26; -0.10); < 0.001 SMD [95% CI] -0.47 [-0.68; -0.26][d]
Health status (EQ-5D VAS[f])	185	65.3 (19.9)	6.1 (1.5)	173	67.4 (20.2)	2.8 (1.5)	3.31 [0.70; 5.92]; 0.013 SMD [95% CI] 0.26 [0.05; 0.47][d]
Health-related quality of life							
EORTC QLQ-C30[g]							
Global health status	185	60.7 (22.4)	6.1 (1.6)	178	62.3 (21.6)	0.7 (1.6)	5.39 [3.58; 7.21]; < 0.001 SMD [95% CI] 0.61 [0.40; 0.82][d]
Physical functioning	185	74.2 (23.2)	3.5 (1.4)	177	79.7 (19.4)	-0.3 (1.4)	3.82 [1.37; 6.28]; 0.002 SMD [95% CI] 0.32 [0.11; 0.53][d]
Role functioning	185	66.4 (30.1)	5.6 (2.1)	178	70.6 (26.2)	0.7 (2.1)	4.89 [1.35; 8.43]; 0.007 SMD [95% CI] 0.28 [0.08; 0.49][d]
Emotional functioning	185	74.6 (20.2)	7.4 (1.6)	178	74.7 (20.6)	2.1 (1.6)	5.31 [2.58; 8.04]; < 0.001 SMD [95% CI] 0.40 [0.19; 0.61][d]
Cognitive functioning	185	83.4 (19.9)	3.7 (1.6)	178	83.6 (18.7)	-2.8 (1.6)	6.50 [4.70; 8.31]; < 0.001 SMD [95% CI] 0.74 [0.53; 0.95][d]
Social functioning	184	72.1 (28.1)	4.0 (2.3)	178	72.9 (24.0)	4.7 (2.3)	-0.74 [-4.17; 2.69]; 0.673

Table 11: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd (multipage table)

Study outcome category outcome	Ciltacabtagene autoleucel			Individualized treatment choosing from DPd or PVd			Ciltacabtagene autoleucel versus individualized treatment, choosing from DPd or PVd
	N[a]	values at baseline mean (SD)	mean change in the course of the study mean[b] (SE)	N[a]	values at baseline mean (SD)	mean change in the course of the study mean[b] (SE)	MD [95% CI]; p-value[b]
MySIm-Q Total Impact Score[c]	185	1.3 (0.9)	-0.3 (0.1)	174	1.2 (0.8)	-0.1 (0.1)	-0.17 [-0.28; -0.05]; 0.004 SMD [95% CI] -0.30 [-0.51; -0.09][d]

a. Number of patients taken into account in the effect estimation; baseline values may rest on different patient numbers.
b. Mean and SE (per treatment group) as well as MD, CI and p-value (group comparison) from MMRM. The effect represents the difference in the changes (from baseline) averaged over the course of the study between the treatment groups.
c. Lower (decreasing) values mean better improved symptoms/quality of life; negative effects mean an advantage for the intervention (scale range: 0 to 100).
d. Institute's calculation based on MD and CI from the MMRM analysis.
e. Lower (decreasing) values mean improved symptoms; a negative effect shows an advantage for the intervention (scale range from "normal, not at all ill" to "severely ill"; in Module 4 A, the company converted the scale for the analyses into numerical values from 1 ["normal, not at all ill"] to 5 ["severely ill"] [4]).
f. Higher (increasing) values mean an improved health status; positive effects mean an advantage for the intervention (scale range 0 to 100).
g. Higher (increasing) values mean better health-related quality of life; positive effects mean an advantage for the intervention (scale range: 0 to 100).

CI: Confidence Interval; DPd: daratumumab in combination with pomalidomide and dexamethasone; EORTC: European Organisation for Research and Treatment of Cancer; MD: mean difference; MMRM: mixed-effects model repeated measures; MySIm-Q: Multiple Myeloma Symptom and Impact Questionnaire; N: number of patients with a baseline value and at least one value during the course of the study; PGIS: Patient Global Impression of Severity; PVd: pomalidomide in combination with bortezomib and dexamethasone; QLQ-C30: Quality of Life Questionnaire - Core 30; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SMD: standardized mean difference; VAS: visual analogue scale