

Daratumumab (newly diagnosed multiple myeloma, ineligible for stem cell transplant)

Addendum to Project A25-108
(dossier assessment)¹

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Table of contents

	Page
List of tables	v
List of figures	vi
List of abbreviations	viii
1 Background	1
2 Assessment	2
2.1 Study characteristics.....	3
2.2 Results	9
2.2.1 Health status outcome (EQ-5D VAS)	9
2.2.2 Risk of bias and certainty of conclusions.....	11
2.2.3 Results	11
2.2.4 Subgroups and other effect modifiers	15
2.3 Probability and extent of added benefit.....	15
2.3.1 Assessment of added benefit at outcome level.....	15
2.3.2 Overall conclusion on added benefit	19
2.4 Summary.....	19
3 References.....	21
Appendix A Kaplan-Meier curves.....	22
A.1 Mortality.....	22
A.2 Morbidity	23
A.2.1 Symptoms (EORTC QLQ-C30)	23
A.2.2 Symptoms (EORTC QLQ-MY20)	31
A.2.3 Health status (EQ-5D VAS).....	33
A.3 Health-related quality of life.....	34
A.3.1 EORTC QLQ-C30	34
A.3.2 EORTC QLQ-MY20.....	40
A.4 Side effects.....	42
Appendix B Results on side effects.....	46
Appendix C Supplementary information on health status (EQ-5D VAS).....	56
C.1 Results	56
C.2 Kaplan-Meier curves.....	57

List of tables

	Page
Table 1: : Information on the course of the study – RCT, direct comparison: daratumumab+ bortezomib + lenalidomide + dexamethasonea vs. bortezomib + lenalidomide + dexamethasoneb, relevant subpopulation	4
Table 2: Study/treatment discontinuation – RCT, direct comparison: daratumumab+ bortezomib + lenalidomide + dexamethasone vs. bortezomib + lenalidomide + dexamethasone, relevant subpopulation.....	5
Table 3: Information on subsequent antineoplastic therapies (≥ 2 patients in both treatment arms combined) – RCT, direct comparison: daratumumab + bortezomib + lenalidomide + dexamethasone vs. bortezomib + lenalidomide + dexamethasone, relevant subpopulation	7
Table 4: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: daratumumab + bortezomib + lenalidomide + dexamethasone vs. bortezomib + lenalidomide + dexamethasone, relevant subpopulation.....	12
Table 5: Extent of added benefit at outcome level: daratumumab + bortezomib + lenalidomide + dexamethasone vs. bortezomib + lenalidomide + dexamethasone	16
Table 6: Positive and negative effects from the assessment of daratumumab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone	19
Table 7: Daratumumab + bortezomib + lenalidomide + dexamethasone – probability and extent of added benefit.....	20
Table 8: Common AEs – RCT, direct comparison: daratumumab+ bortezomib + lenalidomide + dexamethasone vs. bortezomib + lenalidomide + dexamethasone, relevant subpopulation	47
Table 9: Common SAEs – RCT, direct comparison: daratumumab+ bortezomib + lenalidomide + dexamethasone vs. bortezomib + lenalidomide + dexamethasone, relevant subpopulation	51
Table 10: Common severe AEs (CTCAE grade ≥ 3) – RCT, direct comparison: daratumumab+ bortezomib + lenalidomide + dexamethasone vs. bortezomib + lenalidomide + dexamethasone, relevant subpopulation.....	52
Table 11: Common discontinuations due to AEs (at least one treatment component) – RCT, direct comparison: daratumumab+ bortezomib + lenalidomide + dexamethasone vs. bortezomib + lenalidomide + dexamethasone, relevant subpopulation.....	54
Table 12: Results on health status (EQ-5D VAS) presented as supplementary information – RCT, direct comparison: daratumumab+ bortezomib + lenalidomide + dexamethasone vs. bortezomib + lenalidomide + dexamethasone, relevant subpopulation.....	56

List of figures

	Page
Figure 1: Kaplan-Meier curves for the outcome overall survival, CEPHEUS (relevant subpopulation), data cut from 8 October 2025	22
Figure 2: Kaplan-Meier curves for the outcome fatigue (EORTC QLQ-C30 – time to first deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025	23
Figure 3: Kaplan-Meier curves for the outcome nausea and vomiting (EORTC QLQ-C30 – time to first deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025	24
Figure 4: Kaplan-Meier curves for the outcome pain (EORTC QLQ-C30 – time to first deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025	25
Figure 5: Kaplan-Meier curves for the outcome dyspnoea (EORTC QLQ-C30 – time to first deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025	26
Figure 6: Kaplan-Meier curves for the outcome insomnia (EORTC QLQ-C30 – time to first deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025	27
Figure 7: Kaplan-Meier curves for the outcome appetite loss (EORTC QLQ-C30 – time to first deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025	28
Figure 8: Kaplan-Meier curves for the outcome constipation (EORTC QLQ-C30 – time to first deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025	29
Figure 9: Kaplan-Meier curves for the outcome diarrhoea (EORTC QLQ-C30 – time to first deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025	30
Figure 10: Kaplan-Meier curves for the outcome disease symptoms (EORTC QLQ-MY20 – time to first deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025	31
Figure 11: Kaplan-Meier curves for the outcome side effects (EORTC QLQ-MY20 – time to first deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025	32
Figure 12: Kaplan-Meier curves for the outcome health status (EQ-5D VAS – time to confirmed permanent deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025	33
Figure 13: Kaplan-Meier curves for the outcome global health status (EORTC QLQ-C30 – time to first deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025	34
Figure 14: Kaplan-Meier curves for the outcome physical functioning (EORTC QLQ-C30 – time to first deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025	35

Figure 15: Kaplan-Meier curves for the outcome role functioning (EORTC QLQ-C30 – time to first deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025	36
Figure 16: Kaplan-Meier curves for the outcome emotional functioning (EORTC QLQ-C30 – time to first deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025	37
Figure 17: Kaplan-Meier curves for the outcome cognitive functioning (EORTC QLQ-C30 – time to first deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025	38
Figure 18: Kaplan-Meier curves for the outcome social functioning (EORTC QLQ-C30 – time to first deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025	39
Figure 19: Kaplan-Meier curves for the outcome future perspective (EORTC QLQ-MY20 – time to first deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025	40
Figure 20: Kaplan-Meier curves for the outcome body image (EORTC QLQ-MY20 – time to first deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025	41
Figure 21: Kaplan-Meier curves for the outcome SAEs, CEPHEUS (relevant subpopulation), data cut from 8 October 2025	42
Figure 22: Kaplan-Meier curves for the outcome severe AEs (CTCAE grade ≥ 3), CEPHEUS (relevant subpopulation), data cut from 8 October 2025	43
Figure 23: Kaplan-Meier curves for the outcome discontinuation due to AEs (at least one treatment component), CEPHEUS (relevant subpopulation), data cut from 8 October 2025	44
Figure 24: Kaplan-Meier curves for the outcome peripheral neuropathy (HLT, severe AEs [CTCAE grade ≥ 3]), CEPHEUS (relevant subpopulation), data cut from 8 October 2025	45
Figure 25: Kaplan-Meier curves for the outcome health status (EQ-5D VAS – time to first deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025	57
Figure 26: Kaplan-Meier curves for the outcome health status (EQ-5D VAS – time to confirmed deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025	58

List of abbreviations

Abbreviation	Meaning
AE	adverse event
ASCT	autologous stem cell transplant
CD	cluster of differentiation
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DGHO	Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (German Society for Haematology and Medical Oncology)
EHA	European Hematology Association
EMA	European Medicines Agency
EMN	European Myeloma Network
EORTC	European Organisation for Research and Treatment of Cancer
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HLT	High Level Term
IMWG	International Myeloma Working Group
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
PFS	progression-free survival
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-MY20	Quality of Life Questionnaire-Multiple Myeloma 20
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
VAS	visual analogue scale

1 Background

On 13 January 2026, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A25-108 (Daratumumab [newly diagnosed multiple myeloma, ineligible for stem cell transplant]– Benefit assessment according to §35a Social Code Book V) [1].

The commission comprised the assessment of the analyses presented by the pharmaceutical company (hereinafter referred to as ‘the company’) in the commenting procedure [2,3], taking into account the information provided in the dossier [4]:

- Data subsequently submitted for the final data-cut of the CEPHEUS study from 8 October 2025

The responsibility for this 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) CEPHEUS was included for the benefit assessment of daratumumab in combination with bortezomib, lenalidomide and dexamethasone (hereinafter ‘daratumumab + bortezomib + lenalidomide + dexamethasone’) in adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (ASCT). The CEPHEUS study is an open-label study comparing daratumumab + bortezomib + lenalidomide + dexamethasone versus bortezomib in combination with lenalidomide and dexamethasone (hereinafter ‘bortezomib + lenalidomide + dexamethasone’). Only the subpopulation of patients who are ineligible for stem cell transplant is relevant for the benefit assessment (for the operationalization, see dossier assessment A25-108 [1]).

In Module 4 A of its dossier, the company presented results for the relevant subpopulation for the 7 May 2024 data cut for the final analysis of progression-free survival (PFS), which was used in the assessment of the added benefit. As part of the commenting procedure, the company submitted analyses relating to the relevant subpopulation for the final data cut-off (end of study) on 8 October 2025.

In accordance with Amendment 6 to the study protocol (14 March 2024), data collection was to end 7 years after the last patient had been randomized (originally planned for up to 5 years), or earlier at the sponsor’s discretion. The end of the study was defined as the occurrence of any of the following events (whichever came first):

- When all patients who are still receiving study treatment at the end of data collection have access through another source such as a commercial availability, continued access through a dedicated long-term extension study, or a patient access programme
- When all patients have discontinued daratumumab treatment
- 31 October 2028

In Module 4 A of the dossier, the company stated that the final data cut-off was expected on 1 September 2026. The end of the study and the final data cut provided by the company in its comments were now dated 8 October 2025, however. In its comments and during the oral hearing [5], the company justified this approach on the grounds that the authorization process had been completed with the European Commission’s resolution in April 2025 and that, consequently, further queries from the European Medicines Agency (EMA) could be ruled out. According to the company, the date chosen for the final data cut-off was 6 years after randomization of the last patient, and this enabled the primary outcome (minimal residual disease [MRD] negativity rate) to be recorded at Month 72 for all remaining patients in the CEPHEUS study. According to the company, the clinical study report (CSR) was not yet available and was expected in March 2026.

The 8 October 2025 data cut, which the company submitted as part of its comments, was not assumed to be event-driven. The data cut provided by the company at the end of the study on 8 October 2025 was the final analysis of the CEPHEUS study and thus covered the longest observation period. The data subsequently submitted by the company were therefore used for this addendum.

Furthermore, in its comments, the company provided the missing data on treatment and study discontinuations for the relevant subpopulation, as well as information on subsequent therapies, and submitted further operationalizations regarding the deterioration in health status (recorded using the EQ-5D visual analogue scale [VAS]).

In accordance with the commission, the following sections contain an assessment of the results of the final, end-of-study data cut from 8 October 2025 for the relevant population of the CEPHEUS study.

2.1 Study characteristics

A detailed description of the CEPHEUS study can be found in dossier assessment A25-108.

Course of the study

Table 1 shows the median treatment duration of the patients in the relevant subpopulation and the median observation period for individual outcomes. In the comments, the company did not provide any information on the mean treatment duration or the mean observation period for individual outcomes for the relevant subpopulation.

Table 1: : Information on the course of the study – RCT, direct comparison: daratumumab+ bortezomib + lenalidomide + dexamethasonea vs. bortezomib + lenalidomide + dexamethasoneb, relevant subpopulation

Study Duration of the study phase Outcome category/outcome	daratumumab + bortezomib + lenalidomide + dexamethasone ^a N = 144	bortezomib + lenalidomide + dexamethasone ^b N = 145
CEPHEUS (data cut: 8 October 2025)		
Treatment duration [months]		
Median [min; max]	57.1 [ND]	34.0 [ND]
Mean (SD)	ND	ND
Observation period [months]		
Overall survival ^c		
Median [min; max]	76.0 [ND]	76.0 [ND]
Mean (SD)	ND	ND
Morbidity, health-related quality of life		
EORTC QLQ-C30		
Median [min; max]	58.9 [ND]	39.7 [ND]
Mean (SD)	ND	ND
EORTC QLQ-MY20		
Median [min; max]	58.9 [ND]	39.7 [ND]
Mean (SD)	ND	ND
EQ-5D VAS		
Median [min; max]	61.9 [ND]	59.2 [ND]
Mean (SD)	ND	ND
Side effects		
Median [min; max]	58.0 [ND]	35.0 [ND]
Mean (SD)	ND	ND
a. Followed by treatment with daratumumab + lenalidomide + dexamethasone in Cycle 9 and beyond. b. Followed by treatment with lenalidomide + dexamethasone in Cycle 9 and beyond. c. Calculated using the inverse Kaplan-Meier method. EORTC: European Organisation for Research and Treatment of Cancer; max: maximum; min: minimum; N: number of analysed patients; ND: no data; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma 20; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale		

For the relevant subpopulation, the median treatment duration at the final data cut-off at the end of the study in the CEPHEUS study was notably longer in the intervention arm (57 months) than in the comparator arm (34 months).

The median observation period for the outcome of overall survival was comparable between the treatment arms (76 months in each case). The observation period between the treatment arms was also comparable for the outcome health status (recorded using the EQ-5D VAS) (intervention vs. comparator arm: 62 months versus 59 months). Since the observation periods for the outcomes in the categories of morbidity (except EQ-5D VAS), health-related quality of life and side effects were linked to the treatment duration (see dossier assessment A25-108 for information on the planned follow-up period for the CEPHEUS study), the median observation periods for these outcomes were notably longer in the intervention arm than in the comparator arm (intervention versus comparator arm: 58 to 59 months versus 35 to 40 months).

Treatment and study discontinuations

Table 2 shows the treatment and study discontinuations in the relevant subpopulation.

Table 2: Study/treatment discontinuation – RCT, direct comparison: daratumumab+ bortezomib + lenalidomide + dexamethasone^a vs. bortezomib + lenalidomide + dexamethasone^b, relevant subpopulation

Study Characteristic	daratumumab + bortezomib + lenalidomide + dexamethasone ^a N ^c = 144	bortezomib + lenalidomide + dexamethasone ^b N ^c = 145
CEPHEUS (data cut: 8 October 2025)		
Treatment discontinuation, n (%) ^d	89 (62)	116 (80 ^e)
Study discontinuation, n (%) ^f	58 (40)	58 (40 ^e)
a. Followed by treatment with daratumumab + lenalidomide + dexamethasone in Cycle 9 and beyond. b. Followed by treatment with lenalidomide + dexamethasone in Cycle 9 and beyond. c. Number of randomized patients in the relevant subpopulation. d. Common reasons for treatment discontinuation in the intervention vs. the comparator arm were disease progression (19% vs. 32%), AE (11% vs. 23%) and patient decision (10 % vs. 6 %). In addition, 0 vs. 3 (2%) of the randomized patients never started treatment. The data additionally include patients who died during the course of the study (intervention arm: 17% vs. comparator arm: 12%). e. Institute's calculation. f. Common reasons for study discontinuation in the intervention vs. the comparator arm were patient decision (8 % vs. 6 %) and lost to follow-up (1 % vs. 1 %). The data additionally include patients who died during the course of the study (intervention arm: 31% vs. comparator arm: 32%). n: number of patients in the category; N: number of randomized patients in the relevant subpopulation; RCT: randomized controlled trial		

There was a difference in treatment discontinuations between the treatment arms (intervention arm versus comparator arm: 62% versus 80%). This difference was due in particular to the higher proportion of disease progression (intervention versus comparator arm: 19% versus 32%) and adverse events (AEs) (intervention versus comparator arm: 11% versus 23%) as a reason for treatment discontinuation in the comparator arm. The proportion

of patients who discontinued the study was comparable across the treatment arms (40% in each).

Subsequent therapies

Table 3 shows the subsequent antineoplastic therapies patients in the relevant subpopulation received after discontinuing the study medication.

Table 3: Information on subsequent antineoplastic therapies (≥ 2 patients in both treatment arms combined) – RCT, direct comparison: daratumumab + bortezomib + lenalidomide + dexamethasone^a vs. bortezomib + lenalidomide + dexamethasone^b, relevant subpopulation (multipage table)

Study Drug	Patients with subsequent therapy, n (%)	
	daratumumab + bortezomib + lenalidomide + dexamethasone ^a N = 144	bortezomib + lenalidomide + dexamethasone ^b N = 145
CEPHEUS (data cut: 8 October 2025)		
Proportion of randomized patients with at least 1 subsequent therapy	25 (17.4 ^c)	61 (42.1 ^c)
Proportion of randomized patients with at least 2 subsequent therapies	12 (8.3 ^c)	22 (15.2 ^c)
1st subsequent therapy ^d		
carfilzomib-dexamethasone	4 (16.0 ^c)	1 (1.6 ^c)
daratumumab-dexamethasone- lenalidomide	3 (12.0 ^c)	4 (6.6 ^c)
bortezomib-dexamethasone- pomalidomide	2 (8.0 ^c)	1 (1.6 ^c)
carfilzomib-dexamethasone- pomalidomide	2 (8.0 ^c)	0 (0)
dexamethasone-isatuximab- pomalidomide	2 (8.0 ^c)	3 (4.9 ^c)
investigational antineoplastic drugs	2 (8.0 ^c)	3 (4.9 ^c)
bortezomib-cyclophosphamide- dexamethasone	1 (4.0 ^c)	1 (1.6 ^c)
bortezomib-dexamethasone	1 (4.0 ^c)	1 (1.6 ^c)
bortezomib-melphalan-prednisone	1 (4.0 ^c)	1 (1.6 ^c)
dexamethasone-ixazomib-lenalidomide	1 (4.0 ^c)	1 (1.6 ^c)
bortezomib-daratumumab- dexamethasone	0 (0)	9 (14.8 ^c)
carfilzomib-daratumumab- dexamethasone	0 (0)	2 (3.3 ^c)
carfilzomib-dexamethasone-isatuximab	0 (0)	2 (3.3 ^c)
daratumumab-dexamethasone	0 (0)	2 (3.3 ^c)
daratumumab-dexamethasone- pomalidomide	0 (0)	3 (4.9 ^c)
dexamethasone-lenalidomide	0 (0)	2 (3.3 ^c)
dexamethasone-pomalidomide	0 (0)	3 (4.9 ^c)
lenalidomide	0 (0)	2 (3.3 ^c)

Table 3: Information on subsequent antineoplastic therapies (≥ 2 patients in both treatment arms combined) – RCT, direct comparison: daratumumab + bortezomib + lenalidomide + dexamethasone^a vs. bortezomib + lenalidomide + dexamethasone^b, relevant subpopulation (multipage table)

Study Drug	Patients with subsequent therapy, n (%)	
	daratumumab + bortezomib + lenalidomide + dexamethasone ^a N = 144	bortezomib + lenalidomide + dexamethasone ^b N = 145
2nd subsequent therapy		
carfilzomib-dexamethasone	1 (8.3 ^c)	1 (4.5 ^c)
investigational antineoplastic drugs	1 (8.3 ^c)	1 (4.5 ^c)
cyclophosphamide-dexamethasone-pomalidomide	1 (8.3 ^c)	1 (4.5 ^c)
carfilzomib-daratumumab-dexamethasone	1 (8.3 ^c)	1 (4.5 ^c)
daratumumab	0 (0)	2 (9.0 ^c)
daratumumab-dexamethasone-pomalidomide	0 (0)	2 (9.0 ^c)
dexamethasone-elotuzumab-pomalidomide	1 (8.3 ^c)	1 (4.5 ^c)
a. Followed by treatment with daratumumab + lenalidomide + dexamethasone in Cycle 9 and beyond. b. Followed by treatment with lenalidomide + dexamethasone in Cycle 9 and beyond. c. Institute's calculation. d. The following percentages relate to patients with at least 1 subsequent therapy. e. The following percentages relate to patients with at least 2 subsequent therapies. n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial		

Based on information on the final end-of-study data cut from 8 October 2025, in the relevant subpopulation, 25 (17%) of the patients in the intervention arm and 61 (42%) of the patients in the comparator arm received at least one subsequent therapy. In its comments, the company stated that 48 PFS events (26 due to progression and 22 due to death) occurred in the intervention arm, and 73 PFS events (56 due to progression and 17 due to death) occurred in the comparator arm. According to the company, 51 patients with disease progression received subsequent therapy. Consequently, in the comparator arm, 5 patients with disease progression did not receive any subsequent therapy. According to the company, the proportion of patients with progression who did not receive subsequent therapy was only 8.9%, but it was still assumed that the subsequent therapies administered in CEPHEUS did not adequately reflect the current standard of care. This is explained below.

As described in dossier assessment A25-108, the treatments administered in the intervention and comparator arm (including cluster of differentiation [CD]38 antibodies,

immunomodulators and proteasome inhibitors) overall reflected the diversity of treatment options in the therapeutic indication. However, some treatments were administered that did not comply with the recommendations of the current German and European guidelines [6,7] (such as subsequent therapy with lenalidomide or carfilzomib as monotherapy).

As explained in dossier assessment A25-108, patients with disease progression during the course of the CEPHEUS study were assumed to be refractory to lenalidomide (and potentially also to the other treatment components of the study medication). In such a situation (patients who are refractory to lenalidomide and have not been pretreated with a CD38 antibody), the German Society for Haematology and Medical Oncology (DGHO) recommends treatment with a CD38 antibody (daratumumab or isatuximab) in combination with dexamethasone and an immunomodulator (pomalidomide) or with dexamethasone and a proteasome inhibitor (carfilzomib or bortezomib) [6]. The guideline recommendations of the European Hematology Association (EHA) and the European Myeloma Network (EMN) also include a CD38 antibody (daratumumab or isatuximab) in combination with dexamethasone and the proteasome inhibitor carfilzomib [7].

In the comparator arm, only 56% (34 out of 61) of the patients with at least one subsequent therapy received treatment with a CD38 antibody (daratumumab or isatuximab) in the first subsequent therapy. Assuming that the patients with disease progression were refractory to lenalidomide (see above), only 31% (19 of 61) of the patients in the comparator arm received an appropriate first subsequent therapy using a CD38 antibody in accordance with the DGHO treatment recommendations.

As set out in dossier assessment A25-108, which was based on data from the previous data cut of 7 May 2024, based on the available data, it was overall still assumed that the subsequent therapies administered in CEPHEUS did not adequately reflect the current standard of care. Analogous to dossier assessment A25-108, the deficiencies regarding the subsequent therapies used were taken into account for the outcomes overall survival and health status (EQ-5D VAS) in the assessment of the outcome-specific risk of bias (see dossier assessment A25-108 and Section 2.2.2 below).

2.2 Results

2.2.1 Health status outcome (EQ-5D VAS)

Regarding the health status outcome (assessed using the EQ-5D VAS), the company's comments included post-hoc responder analyses for the time to deterioration, described by the company as 'confirmed', 'permanent' or 'confirmed permanent', using a defined response threshold of ≥ 15 points (scale range of 0 to 100).

According to the company, these operationalizations of health status deterioration (EQ-5D VAS) were defined as follows:

- Time to confirmed deterioration: operationalized as deterioration in 2 or more consecutive recordings compared with baseline.
- Time to permanent deterioration: operationalized as deterioration observed in one recording and in all subsequent recordings up to the end of the observation period, compared with baseline.
- Time to confirmed permanent deterioration: operationalized as deterioration observed in at least 2 recordings and, in case of further recordings, in all subsequent recordings up to the end of the observation period, compared with baseline.

The company stated that the proportion of patients who had only a single deterioration since the last observation point was > 10% (although it remained unclear to which patients this referred). In accordance with the company's operationalization of the time to permanent deterioration, these patients were recorded as an event and were therefore classified as patients with permanent deterioration. In such cases, however, there was no permanent deterioration, but only one single deterioration. Given the available data, the operationalization of permanent deterioration presented by the company was therefore not suitable for the benefit assessment.

The operationalization of first deterioration initially submitted by the company in the dossier and used in the dossier assessment, as well as the operationalization of confirmed deterioration submitted in the commenting procedure, were in principle suitable for the benefit assessment. However, given the available data and a comparable observation period for the health status outcome, the confirmed permanent deterioration subsequently submitted by the company represented the course of disease more accurately, as it took all recordings into account and thus represented a deterioration that persisted over a longer period of time. The operationalization of confirmed permanent deterioration was a combination of confirmed and permanent deterioration, whereby the threshold value had to be exceeded in at least 2 recordings and in all subsequent recordings, if any, until the end of the observation period in order to be classified as an event. Patients with only a single deterioration at the last observation point, however, were not counted as an event. This was appropriate.

This benefit assessment used the responder analyses for the time to confirmed permanent deterioration of ≥ 15 points submitted by the company (see Table 4 in Section 2.2.3). The responder analyses presented by the company for the time to first deterioration and the time to confirmed deterioration of ≥ 15 points in each case are provided as supplementary information in Appendix C of this addendum. As described above, the operationalization

provided by the company for the time to permanent deterioration was not appropriate and is therefore not presented.

2.2.2 Risk of bias and certainty of conclusions

In comparison with dossier assessment A25-108, the classification in this addendum remains unchanged for both the risk of bias across outcomes and the outcome-specific risk of bias of the CEPHEUS study.

Regarding the results in the outcomes of overall survival and health status (EQ-5D VAS), as in dossier assessment A25-108, the impact of the inadequate subsequent therapies (see Section 2.1) on the observed effects remained unclear.

With regard to the results for the health status outcome (EQ-5D VAS), the reasons for the high risk of bias described in the dossier assessments continued to be applicable: lack of blinding in subjective recording of outcomes, large proportion of patients (> 10%) not considered in the analysis, and uncertainties due to the appropriate use of subsequent therapies.

Irrespective of this, the certainty of conclusions of the study results was reduced due to the uncertainties described in dossier assessment A25-108 regarding ASCT ineligibility of the relevant subpopulation included. The results of the CEPHEUS study can therefore at most be used to derive hints, for example of an added benefit.

2.2.3 Results

Table 4 summarizes the results of the comparison of daratumumab + bortezomib + lenalidomide + dexamethasone with bortezomib + lenalidomide + dexamethasone in patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplantation. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's comments.

The Kaplan-Meier curves for the time-to-event analyses of the outcomes in the included CEPHEUS study are shown in Appendix A. The results on common AEs, serious adverse events (SAEs), severe AEs and discontinuations due to AEs can be found in Appendix B.

Table 4: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: daratumumab + bortezomib + lenalidomide + dexamethasone^a vs. bortezomib + lenalidomide + dexamethasone^b, relevant subpopulation (multipage table)

Study Outcome category Outcome	daratumumab + bortezomib + lenalidomide + dexamethasone ^a		bortezomib + lenalidomide + dexamethasone ^b		daratumumab + bortezomib + lenalidomide + dexamethasone ^a vs. bortezomib + lenalidomide + dexamethasone ^b
	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 ^c
CEPHEUS (data cut: 8 October 2025)					
Mortality					
Overall survival	144	NA 48 (33.3)	145	NA [78.1; NA] 53 (36.6)	0.84 [0.57; 1.24]; 0.378
Morbidity					
Symptoms (EORTC QLQ-C30 – time to first deterioration) ^{d, e}					
Fatigue	138	1.4 [1.0; 1.7] 100 (72.5 ^f)	137	1.5 [1.5; 2.2] 103 (75.2 ^f)	1.08 [0.81; 1.44]; 0.599
Nausea and vomiting	138	6.0 [4.2; 16.9] 85 (61.6 ^f)	137	11.4 [4.5; 45.5] 70 (51.1 ^f)	1.23 [0.89; 1.70]; 0.207
Pain	138	3.7 [2.3; 8.3] 79 (57.2 ^f)	137	3.5 [2.8; 4.0] 88 (64.2 ^f)	0.91 [0.67; 1.24]; 0.560
Dyspnoea	138	3.1 [2.2; 3.7] 101 (73.2 ^f)	137	5.3 [2.9; 11.1] 88 (64.2 ^f)	1.23 [0.92; 1.65]; 0.160
Insomnia	138	2.8 [1.8; 3.9] 102 (73.9 ^f)	137	2.8 [2.2; 4.2] 93 (67.9 ^f)	1.04 [0.78; 1.39]; 0.783
Appetite loss	138	4.4 [3.5; 5.1] 100 (72.5 ^f)	137	3.6 [2.6; 4.6] 97 (70.1 ^f)	0.93 [0.70; 1.24]; 0.634
Constipation	138	3.1 [1.6; 5.6] 94 (68.1 ^f)	137	1.6 [1.4; 2.4] 106 (77.4 ^f)	0.69 [0.51; 0.92]; 0.011
Diarrhoea	138	4.7 [3.5; 6.0] 117 (84.8 ^f)	137	3.7 [2.8; 4.4] 108 (78.8 ^f)	0.91 [0.70; 1.20]; 0.502
Symptoms (EORTC QLQ-MY20 – time to first deterioration) ^{d, e}					
Disease symptoms	136	11.6 [4.6; 26.9] 73 (53.7 ^f)	135	13.9 [7.5; 28.2] 78 (57.8 ^f)	1.07 [0.77; 1.48]; 0.699
Side effects	136	2.4 [2.1; 3.5] 99 (72.8 ^f)	135	2.9 [2.1; 4.2] 94 (69.6 ^f)	1.17 [0.88; 1.57]; 0.279
Health status (EQ-5D VAS – time to confirmed permanent deterioration) ^{e, g, h}	121	NA 15 (12.4 ^f)	125	NA 27 (21.6 ^f)	0.43 [0.23; 0.81]; 0.009

Table 4: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: daratumumab + bortezomib + lenalidomide + dexamethasone^a vs. bortezomib + lenalidomide + dexamethasone^b, relevant subpopulation (multipage table)

Study Outcome category Outcome	daratumumab + bortezomib + lenalidomide + dexamethasone ^a		bortezomib + lenalidomide + dexamethasone ^b		daratumumab + bortezomib + lenalidomide + dexamethasone ^a vs. bortezomib + lenalidomide + dexamethasone ^b
	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 ^c
Health-related quality of life					
EORTC QLQ-C30 – time to first deterioration ^{e, i}					
Global health status	138	2.1 [1.6; 3.2] 86 (62.3 ^f)	137	2.8 [2.2; 4.4] 82 (59.9 ^f)	1.19 [0.87; 1.63]; 0.274
Physical functioning	138	3.0 [1.7; 4.3] 90 (65.2 ^f)	137	3.5 [2.8; 4.5] 92 (67.2 ^f)	1.11 [0.83; 1.50]; 0.484
Role functioning	138	2.1 [1.5; 3.1] 89 (64.5 ^f)	137	2.8 [2.1; 3.6] 92 (67.2 ^f)	1.04 [0.77; 1.40]; 0.819
Emotional functioning	138	9.3 [3.3; 23.3] 75 (54.3 ^f)	137	5.3 [3.5; 12.5] 83 (60.6 ^f)	0.88 [0.63; 1.21]; 0.420
Cognitive functioning	138	2.6 [1.8; 3.5] 105 (76.1 ^f)	137	3.5 [2.3; 4.9] 104 (75.9 ^f)	1.18 [0.89; 1.57]; 0.244
Social functioning	138	2.8 [1.5; 3.3] 92 (66.7 ^f)	137	2.5 [1.8; 3.2] 95 (69.3 ^f)	0.97 [0.72; 1.31]; 0.858
EORTC QLQ-MY20 – time to first deterioration ^{e, i}					
Future perspective	136	8.4 [2.8; 48.5] 69 (50.7 ^f)	135	13.7 [4.2; 36.1] 73 (54.1 ^f)	1.03 [0.74; 1.44]; 0.867
Body image	136	8.7 [3.5; 16.6] 80 (58.8 ^f)	135	11.6 [4.2; 50.5] 66 (48.9 ^f)	1.31 [0.94; 1.83]; 0.105
Side effects					
AEs (supplementary information)	144	0.1 [0.1; 0.3] 144 (100)	142	0.2 [0.1; 0.3] 142 (100)	–
SAEs	144	12.3 [5.5; 22.1] 109 (75.7)	142	8.3 [4.0; 16.6] 99 (69.7)	0.94 [0.72; 1.25]; 0.686
Severe AEs ^j	144	0.9 [0.7; 1.6] 135 (93.8)	142	1.5 [1.0; 2.1] 126 (88.7)	1.05 [0.82; 1.36]; 0.686
Discontinuation due to AEs	144	58.4 [44.3; NA] 67 (46.5)	142	44.2 [26.5; 67.5] 75 (52.8)	0.72 [0.52; 1.003]; 0.052
Peripheral neuropathy (HLT, severe AEs ^j)	144	NA 18 (12.5)	142	NA 16 (11.3)	1.12 [0.57; 2.21]; 0.735

Table 4: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: daratumumab + bortezomib + lenalidomide + dexamethasone^a vs. bortezomib + lenalidomide + dexamethasone^b, relevant subpopulation (multipage table)

Study Outcome category Outcome	daratumumab + bortezomib + lenalidomide + dexamethasone ^a		bortezomib + lenalidomide + dexamethasone ^b		daratumumab + bortezomib + lenalidomide + dexamethasone ^a vs. bortezomib + lenalidomide + dexamethasone ^b
	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 ^c
a. Followed by treatment with daratumumab + lenalidomide + dexamethasone in Cycle 9 and beyond. b. Followed by treatment with lenalidomide + dexamethasone in Cycle 9 and beyond. c. Effect, CI and p-value according to information provided by the company: Cox proportional hazards model; each stratified according to ISS stage (I vs. II vs. III) and age/ASCT eligibility (≥ 70 years vs. < 70 years ASCT ineligible vs. < 70 years and refusal to have ASCT). Patients < 70 years who had refused ASCT were not included in the subpopulation relevant for the benefit assessment, which was analysed here. For the overall survival outcome, the p-value from the corresponding stratified log-rank test is shown. d. A score increase in EORTC QLQ-C30 and EORTC QLQ-MY20 by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100). e. According to Module 4 A, only patients with a baseline value and at least one other value in the course of the study are included in the analyses. f. Institute's calculation. g. The operationalization is a combination of confirmed and permanent deterioration (see Section 2.2.1). h. An EQ-5D VAS score decrease by ≥ 15 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100). i. A score decrease in EORTC QLQ-C30 and EORTC QLQ-MY20 of ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100). j. Operationalized as CTCAE grade ≥ 3. AE: adverse event; ASCT: autologous stem cell transplantation; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HLT: High Level Term; HR: hazard ratio; ISS: International Staging System; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Myeloma Module 20; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale					

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

Based on the data submitted subsequently as part of the company's comments, a statistically significant difference in favour of daratumumab + bortezomib + lenalidomide + dexamethasone compared with bortezomib + lenalidomide + dexamethasone was observed only for the health status outcome (recorded using the EQ-5D VAS, time to confirmed

permanent deterioration). For this outcome, there is a hint of an added benefit of daratumumab + bortezomib + lenalidomide + dexamethasone in comparison with bortezomib + lenalidomide + dexamethasone.

2.2.4 Subgroups and other effect modifiers

As in dossier assessment A25-108, due to the uncertainties regarding the relevant subpopulation included (patients ineligible for ASCT; see explanations in dossier assessment A25-108), the subsequent subgroup analyses were subject to the following uncertainty: It was unknown how patients who were still eligible for ASCT were distributed across possible subgroups and to what extent this would lead to a bias in the subgroup results. The results from the subgroup analyses were therefore assessed as non-interpretable, and no subgroup analyses were used for this benefit assessment.

2.3 Probability and extent of added benefit

2.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in the sections above (see Table 5).

Determination of the outcome category for the morbidity outcomes

It could not be inferred from the dossier whether the following morbidity outcomes were serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Health status (EQ-5D VAS)

For the outcome health status (EQ-5D VAS), insufficient information was available to allow a severity category classification of serious or severe. The outcome of health status (EQ-5D VAS) was therefore allocated to the outcome category of non-serious / non-severe symptoms / late complications.

Constipation (EORTC QLQ-C30)

For the outcome constipation (EORTC QLQ-C30), insufficient severity data were available for a classification as serious/severe. The outcome of constipation (EORTC QLQ-C30) was therefore allocated to the outcome category of non-serious/non-severe symptoms/late complications.

Table 5: Extent of added benefit at outcome level: daratumumab + bortezomib + lenalidomide + dexamethasone^a vs. bortezomib + lenalidomide + dexamethasone^b (multipage table)

Outcome category Outcome	daratumumab + bortezomib + lenalidomide + dexamethasone ^a vs. bortezomib + lenalidomide + dexamethasone ^b Median time to event (months) Effect estimation [95% CI]; p-value Probability ^c	Derivation of extent ^d
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	NA vs. NA HR: 0.84 [0.57; 1.24]; p = 0.378	Lesser benefit not proven / added benefit not proven
Morbidity		
Health status (time to confirmed permanent deterioration by ≥ 15 points)		
EQ-5D VAS	NA vs. NA HR: 0.43 [0.23; 0.81]; p = 0.009 Probability: hint	Outcome category: non-serious/non-severe symptoms/late complications 0.80 ≤ CI _u < 0.90 Added benefit, extent: “minor”
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30 – time to first deterioration by ≥ 10 points)		
Fatigue	1.4 vs. 1.5 HR: 1.08 [0.81; 1.44]; p = 0.599	Lesser benefit not proven / added benefit not proven
Nausea and vomiting	6.0 vs. 11.4 HR: 1.23 [0.89; 1.70]; p = 0.207	Lesser benefit not proven / added benefit not proven
Pain	3.7 vs. 3.5 HR: 0.91 [0.67; 1.24]; p = 0.560	Lesser benefit not proven / added benefit not proven
Dyspnoea	3.1 vs. 5.3 HR: 1.23 [0.92; 1.65]; p = 0.160	Lesser benefit not proven / added benefit not proven
Insomnia	2.8 vs. 2.8 HR: 1.04 [0.78; 1.39]; p = 0.783	Lesser benefit not proven / added benefit not proven
Appetite loss	4.4 vs. 3.6 HR: 0.93 [0.70; 1.24]; p = 0.634	Lesser benefit not proven / added benefit not proven

Table 5: Extent of added benefit at outcome level: daratumumab + bortezomib + lenalidomide + dexamethasone^a vs. bortezomib + lenalidomide + dexamethasone^b (multipage table)

Outcome category Outcome	daratumumab + bortezomib + lenalidomide + dexamethasone ^a vs. bortezomib + lenalidomide + dexamethasone ^b Median time to event (months) Effect estimation [95% CI]; p-value Probability ^c	Derivation of extent ^d
Constipation	3.1 vs. 1.6 HR: 0.69 [0.51; 0.92]; p = 0.011	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Lesser benefit not proven / added benefit not proven ^e
Diarrhoea	4.7 vs. 3.7 HR: 0.91 [0.70; 1.20]; p = 0.502	Lesser benefit not proven / added benefit not proven
Symptoms (EORTC QLQ-MY20 – time to first deterioration by ≥ 10 points)		
Disease symptoms	11.6 vs. 13.9 HR: 1.07 [0.77; 1.48]; p = 0.699	Lesser benefit not proven / added benefit not proven
Side effects	2.4 vs. 2.9 HR: 1.17 [0.88; 1.57]; p = 0.279	Lesser benefit not proven / added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 (time to first deterioration by ≥ 10 points)		
Global health status	2.1 vs. 2.8 HR: 1.19 [0.87; 1.63]; p = 0.274	Lesser benefit not proven / added benefit not proven
Physical functioning	3.0 vs. 3.5 HR: 1.11 [0.83; 1.50]; p = 0.484	Lesser benefit not proven / added benefit not proven
Role functioning	2.1 vs. 2.8 HR: 1.04 [0.77; 1.40]; p = 0.819	Lesser benefit not proven / added benefit not proven
Emotional functioning	9.3 vs. 5.3 HR: 0.88 [0.63; 1.21]; p = 0.420	Lesser benefit not proven / added benefit not proven
Cognitive functioning	2.6 vs. 3.5 HR: 1.18 [0.89; 1.57]; p = 0.244	Lesser benefit not proven / added benefit not proven

Table 5: Extent of added benefit at outcome level: daratumumab + bortezomib + lenalidomide + dexamethasone^a vs. bortezomib + lenalidomide + dexamethasone^b (multipage table)

Outcome category Outcome	daratumumab + bortezomib + lenalidomide + dexamethasone ^a vs. bortezomib + lenalidomide + dexamethasone ^b Median time to event (months) Effect estimation [95% CI]; p-value Probability ^c	Derivation of extent ^d
Social functioning	2.8 vs. 2.5 HR: 0.97 [0.72; 1.31]; p = 0.858	Lesser benefit not proven / added benefit not proven
EORTC QLQ-MY20 (time to first deterioration by ≥ 10 points)		
Future perspective	8.4 vs. 13.7 HR: 1.03 [0.74; 1.44]; p = 0.867	Lesser benefit not proven / added benefit not proven
Body image	8.7 vs. 11.6 HR: 1.31 [0.94; 1.83]; p = 0.105	Lesser benefit not proven / added benefit not proven
Side effects		
SAEs	12.3 vs. 8.3 HR: 0.94 [0.72; 1.25]; p = 0.686	Greater/lesser harm not proven
Severe AEs	0.9 vs. 1.5 HR: 1.05 [0.82; 1.36]; p = 0.686	Greater/lesser harm not proven
Discontinuation due to AEs	58.4 vs. 44.2 HR: 0.72 [0.52; 1.003]; p = 0.052	Greater/lesser harm not proven
Peripheral neuropathy (severe AEs)	NA vs. NA HR: 1.12 [0.57; 2.21]; p = 0.735	Greater/lesser harm not proven
a. Followed by treatment with daratumumab + lenalidomide + dexamethasone in Cycle 9 and beyond. b. Followed by treatment with lenalidomide + dexamethasone in Cycle 9 and beyond. c. Probability provided if there is a statistically significant and relevant effect. d. Estimates of the effect size are made with different limits depending on the outcome category using the upper limit of the confidence interval (CI_u). e. The extent of the effect in this non-serious/non-severe outcome was no more than marginal. AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; NA: not achieved; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma 20; SAE: serious adverse event; VAS: visual analogue scale		

2.3.2 Overall conclusion on added benefit

Table 6 summarizes the results taken into account for the overall conclusion on the extent of the added benefit. The data assessed in this addendum revealed a positive effect compared with the dossier assessment A25-108.

Table 6: Positive and negative effects from the assessment of daratumumab + bortezomib + lenalidomide + dexamethasone^a in comparison with bortezomib + lenalidomide + dexamethasone^b

Positive effects	Negative effects
Outcomes with observation over the entire study duration	
Non-serious / non-severe symptoms / late complications ▪ Health status (EQ-5D VAS): hint of an added benefit – extent: minor	–
Outcomes with shortened observation period	
–	–
a. Followed by treatment with daratumumab + lenalidomide + dexamethasone in Cycle 9 and beyond. b. Followed by treatment with lenalidomide + dexamethasone in Cycle 9 and beyond.	

Overall, there was a positive effect with the extent ‘minor’ for daratumumab + bortezomib + lenalidomide + dexamethasone compared with bortezomib + lenalidomide + dexamethasone only in the health status outcome (EQ-5D VAS). This outcome was observed throughout the entire study duration, and the operationalization presented represented a confirmed or permanent deterioration in the patients’ health status. In summary, given the available data, there is a hint of a minor added benefit of daratumumab + bortezomib + lenalidomide + dexamethasone versus bortezomib + lenalidomide + dexamethasone for adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.

2.4 Summary

The data subsequently submitted by the company in the commenting procedure changed the conclusion on the added benefit of daratumumab + bortezomib + lenalidomide + dexamethasone from dossier assessment A25-108: There is a hint of a minor added benefit of daratumumab + bortezomib + lenalidomide + dexamethasone versus bortezomib + lenalidomide + dexamethasone for adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.

Table 7 below shows the result of the benefit assessment of daratumumab + bortezomib + lenalidomide + dexamethasone, taking into account dossier assessment A25-108 and this addendum.

Table 7: Daratumumab + bortezomib + lenalidomide + dexamethasone – probability and extent of added benefit

Therapeutic indication	ACT ^a	Probability and extent of added benefit
Adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant	▪ daratumumab in combination with lenalidomide and dexamethasone or ▪ daratumumab in combination with bortezomib, melphalan and prednisone or ▪ bortezomib in combination with melphalan and prednisone or ▪ bortezomib in combination with lenalidomide and dexamethasone or ▪ thalidomide in combination with melphalan and prednisone or ▪ bortezomib in combination with cyclophosphamide and dexamethasone (only for patients with peripheral polyneuropathy or an increased risk of developing peripheral polyneuropathy^b)	Hint of minor added benefit
a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company according to the inclusion criteria in Module 4 Section 4.2.2 is printed in bold. b. See Appendix VI to Section K of the Pharmaceutical Directive. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

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

3 References

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Appendix A Kaplan-Meier curves

A.1 Mortality

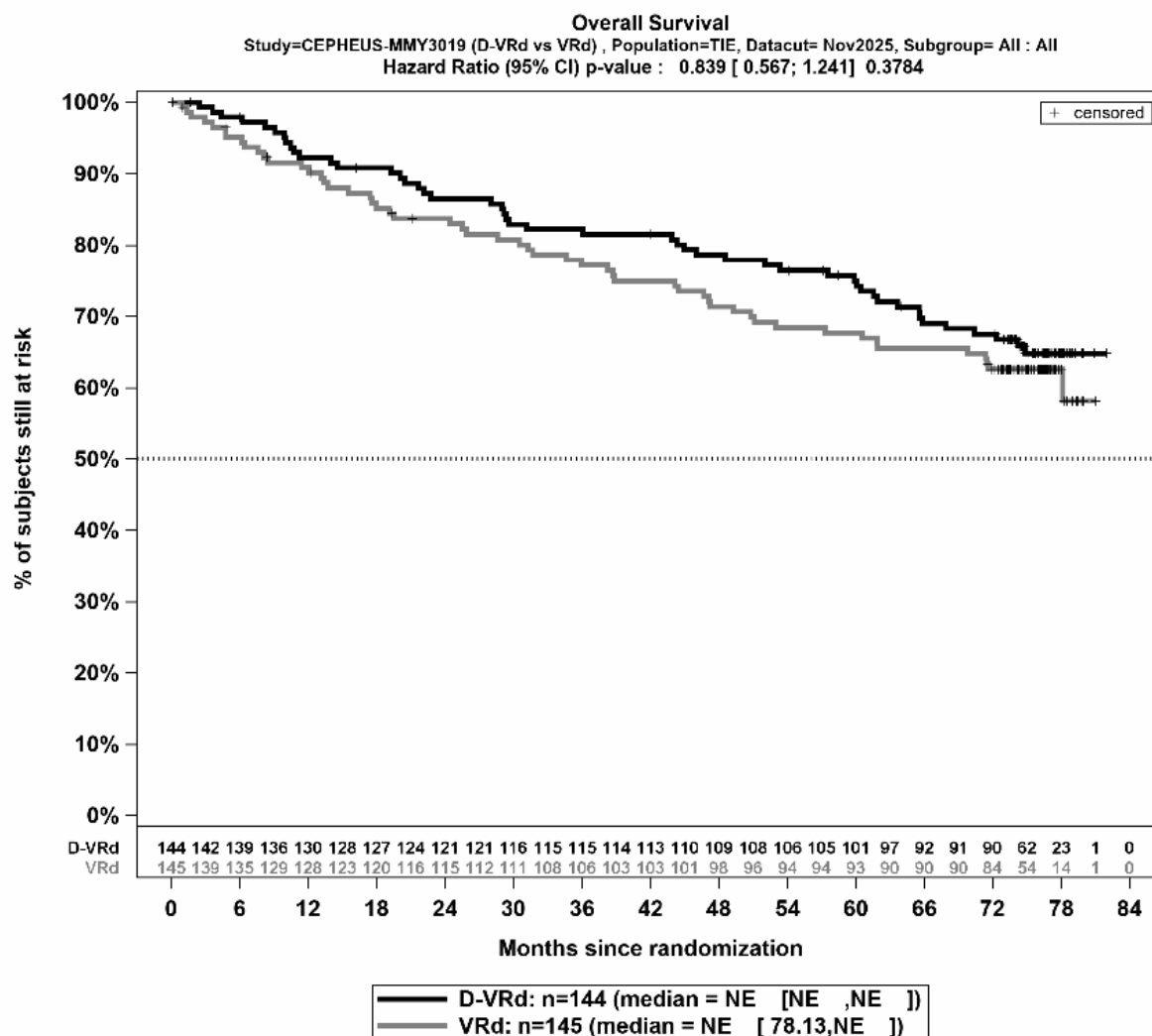


Figure 1: Kaplan-Meier curves for the outcome overall survival, CEPHEUS (relevant subpopulation), data cut from 8 October 2025

A.2 Morbidity

A.2.1 Symptoms (EORTC QLQ-C30)

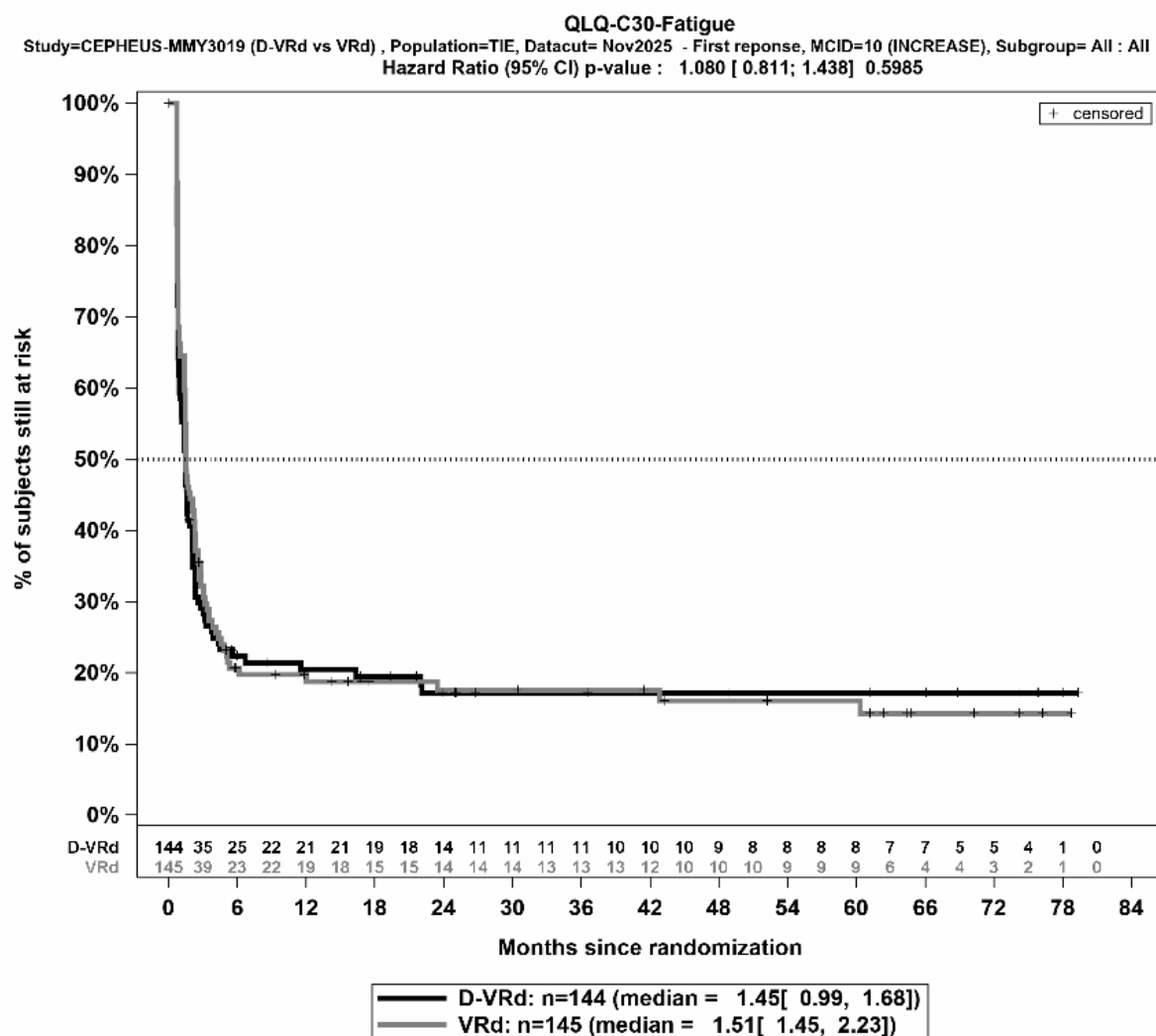


Figure 2: Kaplan-Meier curves for the outcome fatigue (EORTC QLQ-C30 – time to first deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025

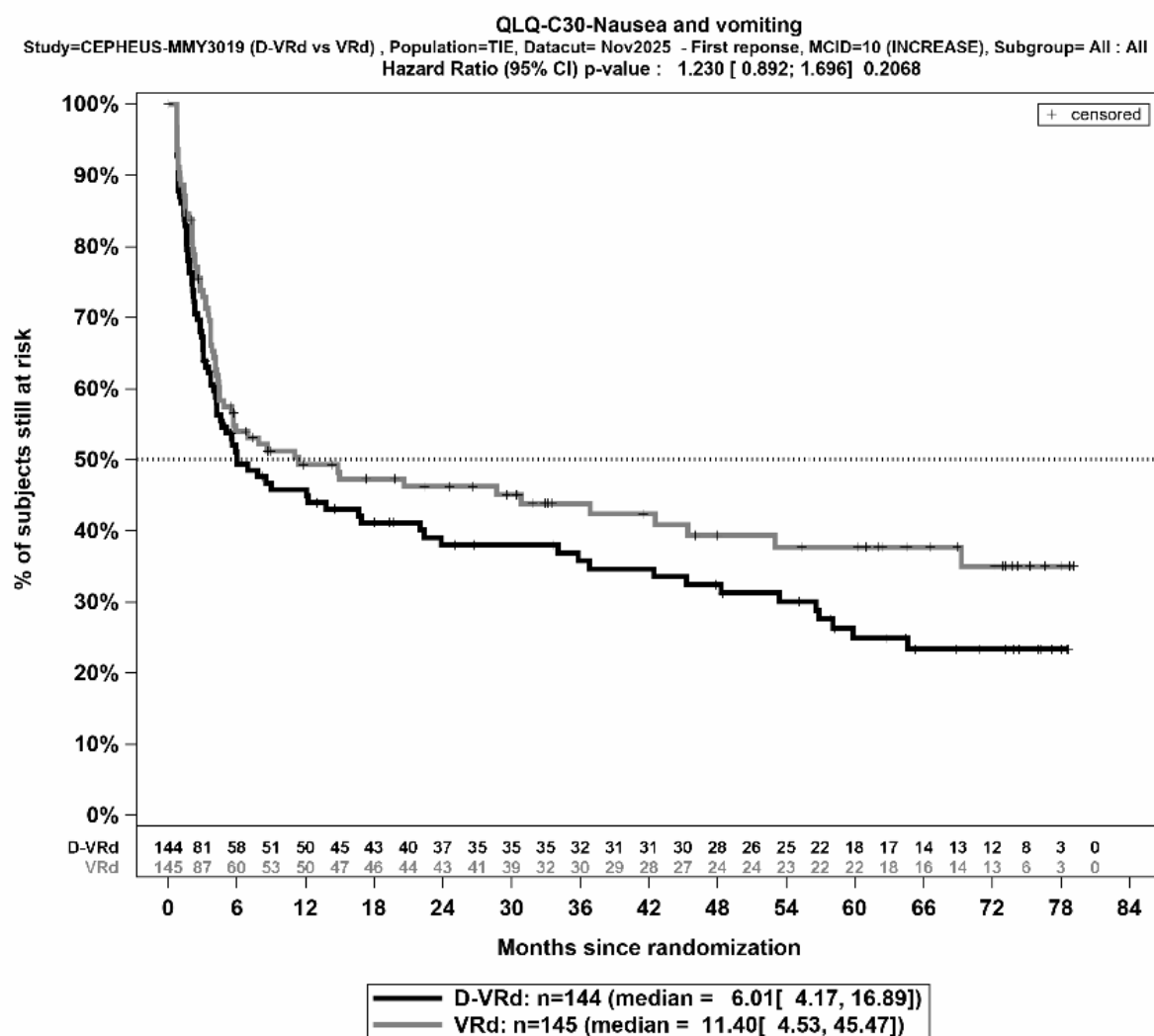


Figure 3: Kaplan-Meier curves for the outcome nausea and vomiting (EORTC QLQ-C30 – time to first deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025

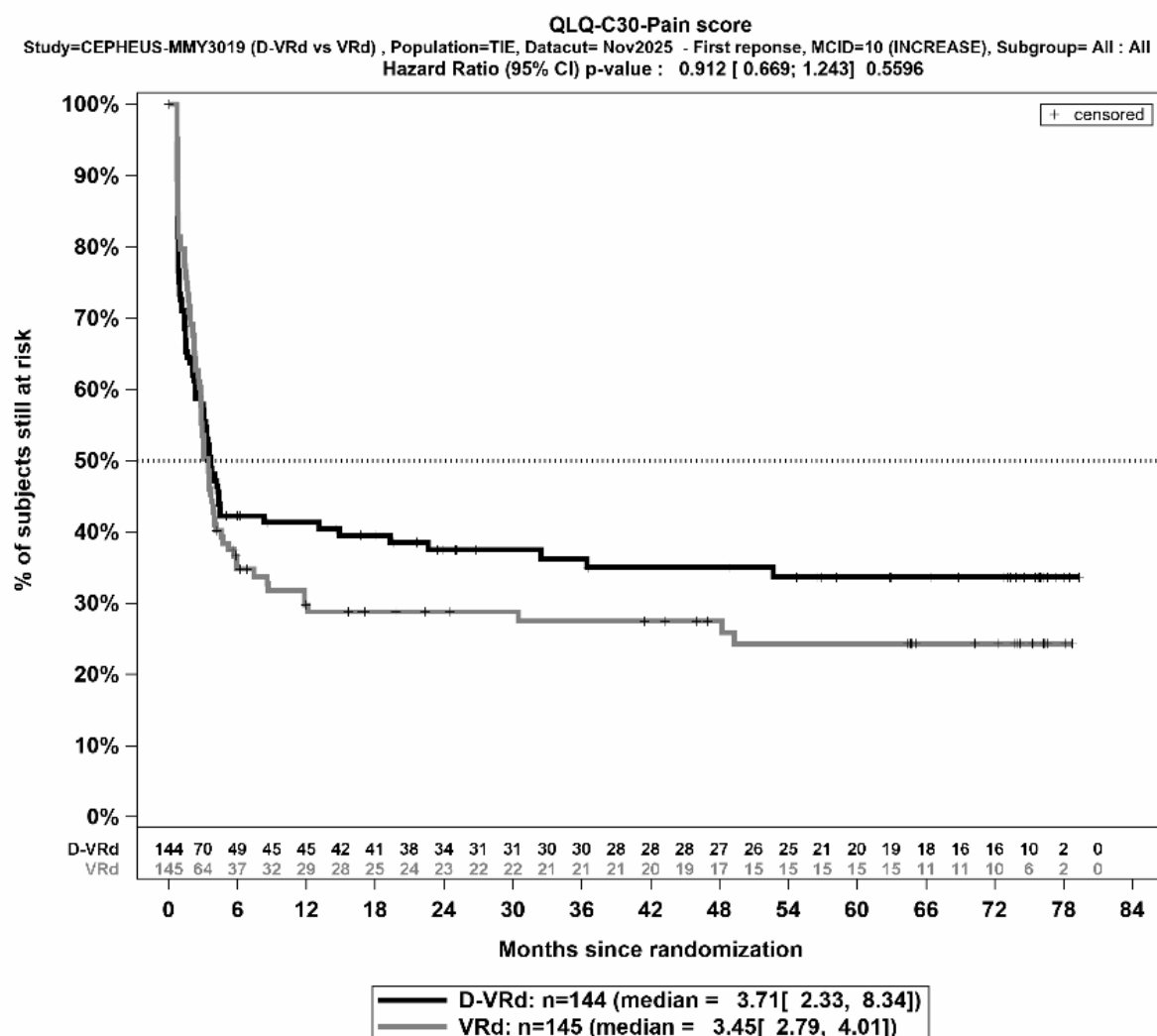


Figure 4: Kaplan-Meier curves for the outcome pain (EORTC QLQ-C30 – time to first deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025

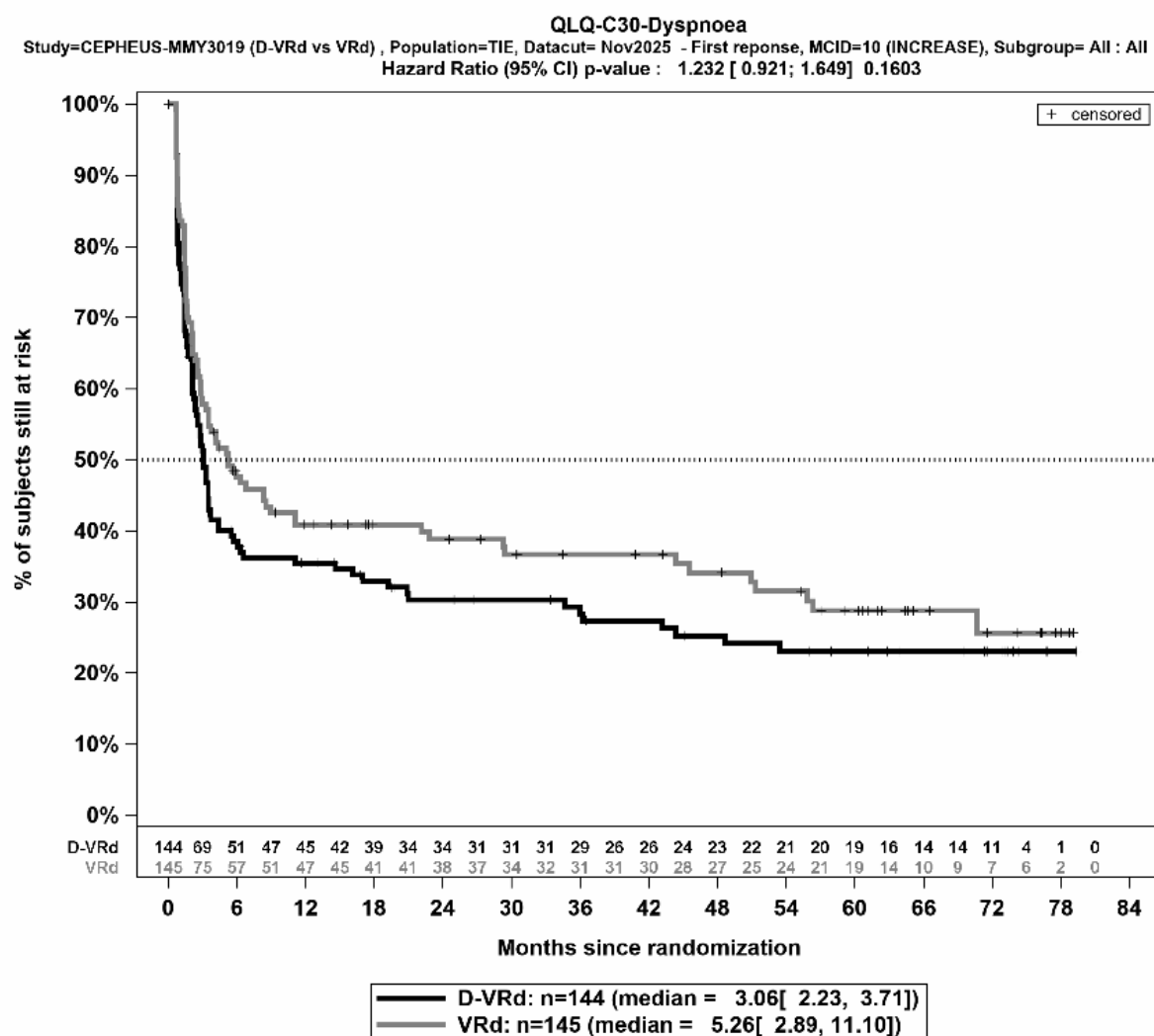


Figure 5: Kaplan-Meier curves for the outcome dyspnoea (EORTC QLQ-C30 – time to first deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025

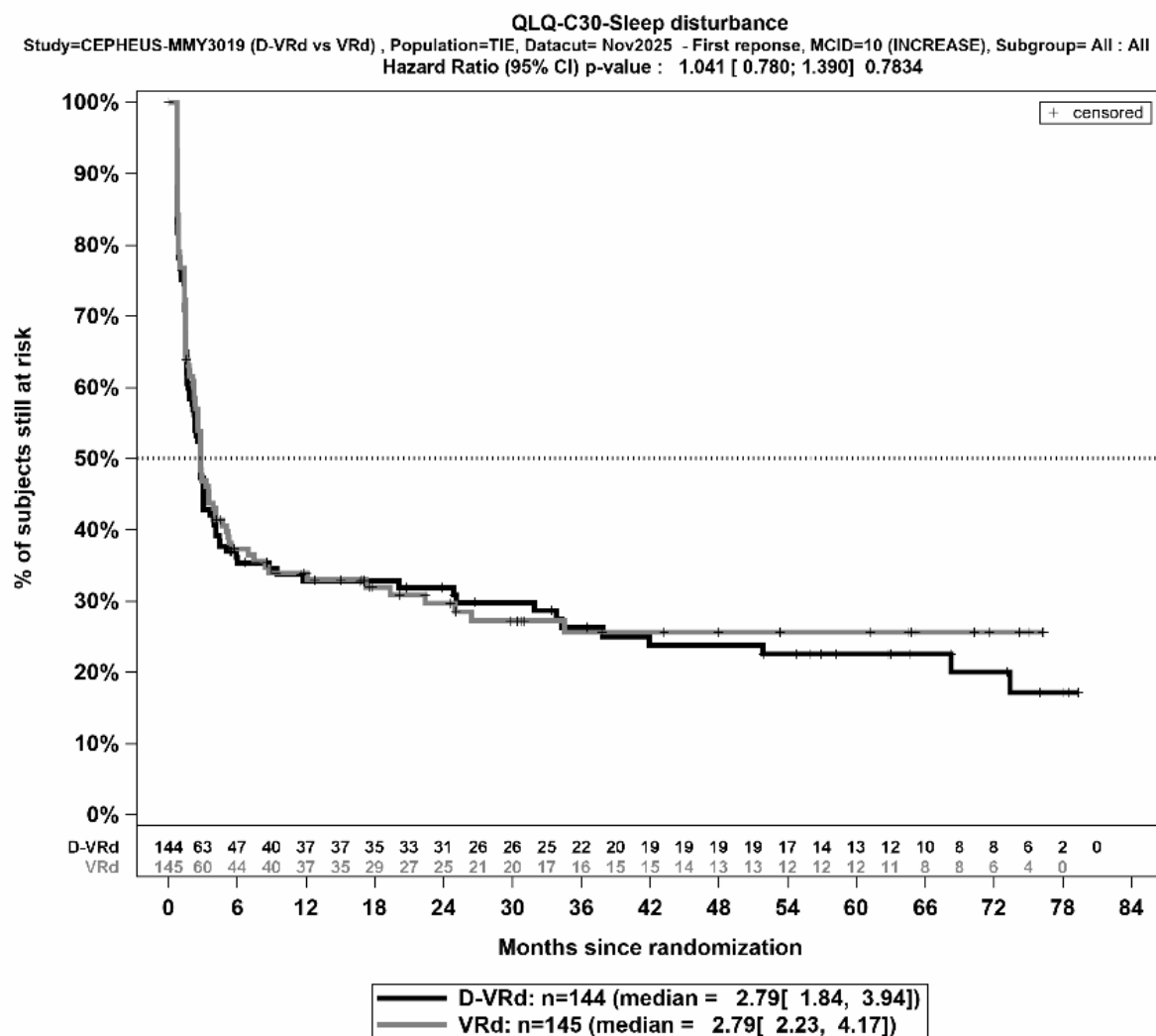


Figure 6: Kaplan-Meier curves for the outcome insomnia (EORTC QLQ-C30 – time to first deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025

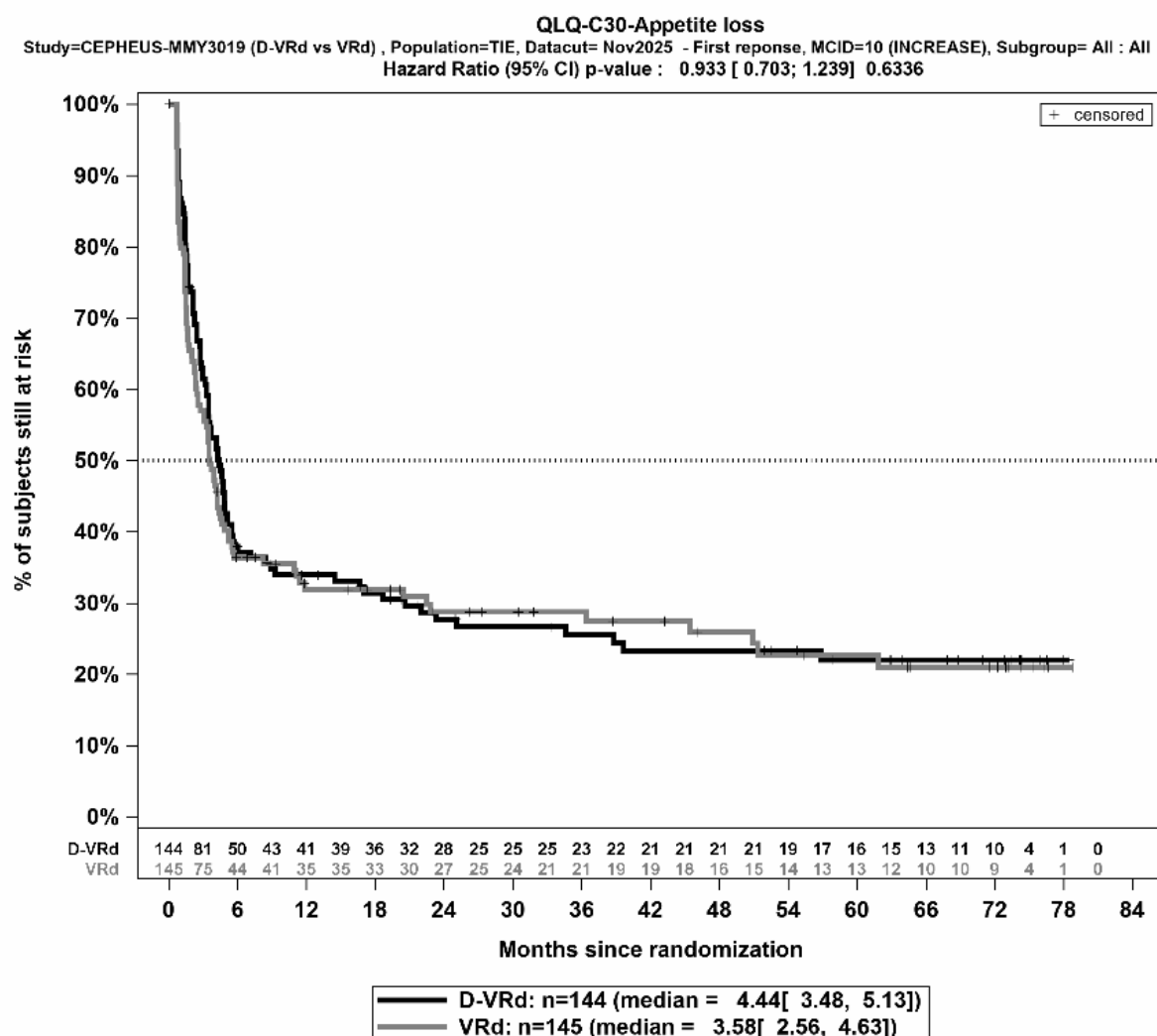


Figure 7: Kaplan-Meier curves for the outcome appetite loss (EORTC QLQ-C30 – time to first deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025

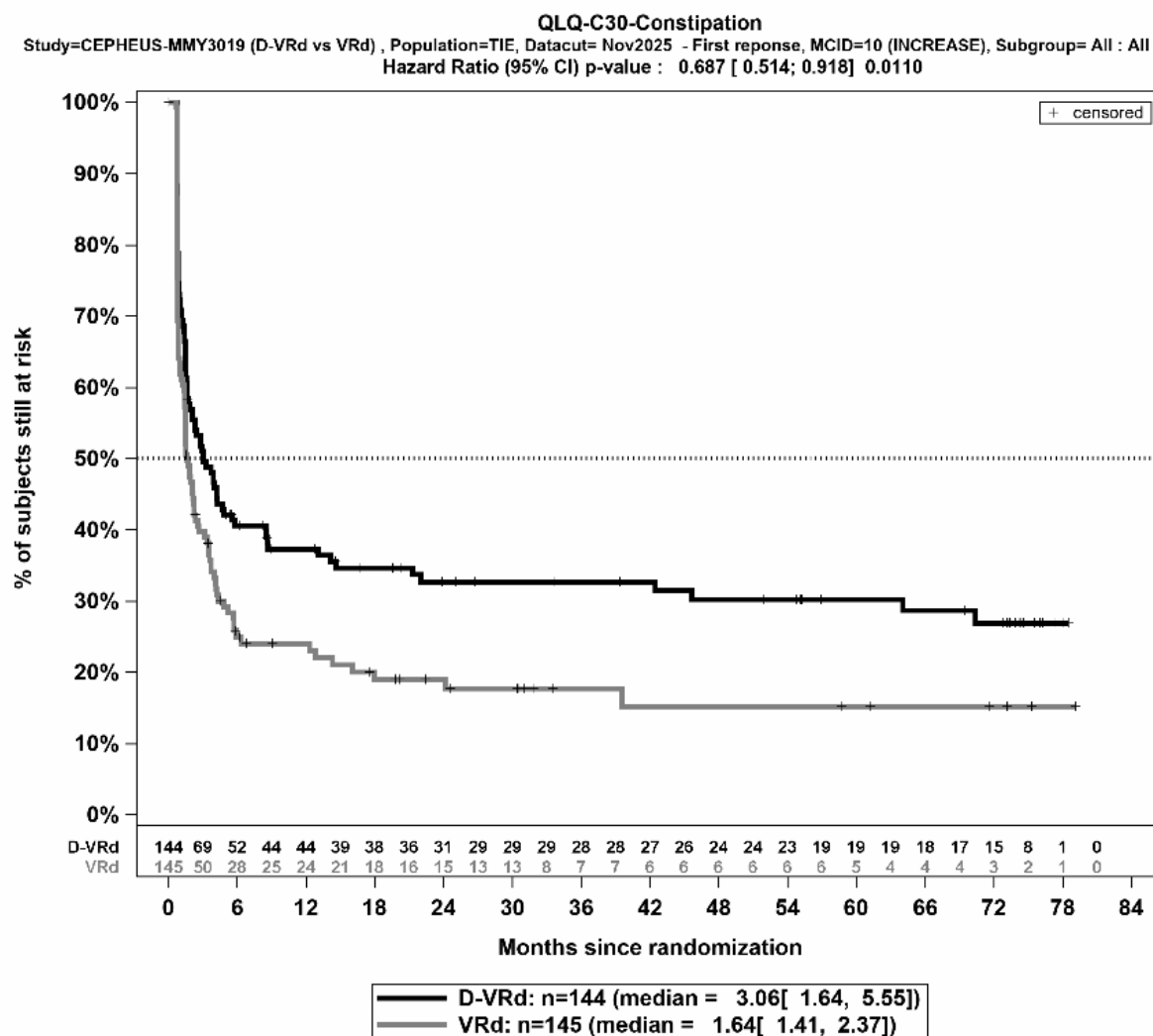


Figure 8: Kaplan-Meier curves for the outcome constipation (EORTC QLQ-C30 – time to first deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025

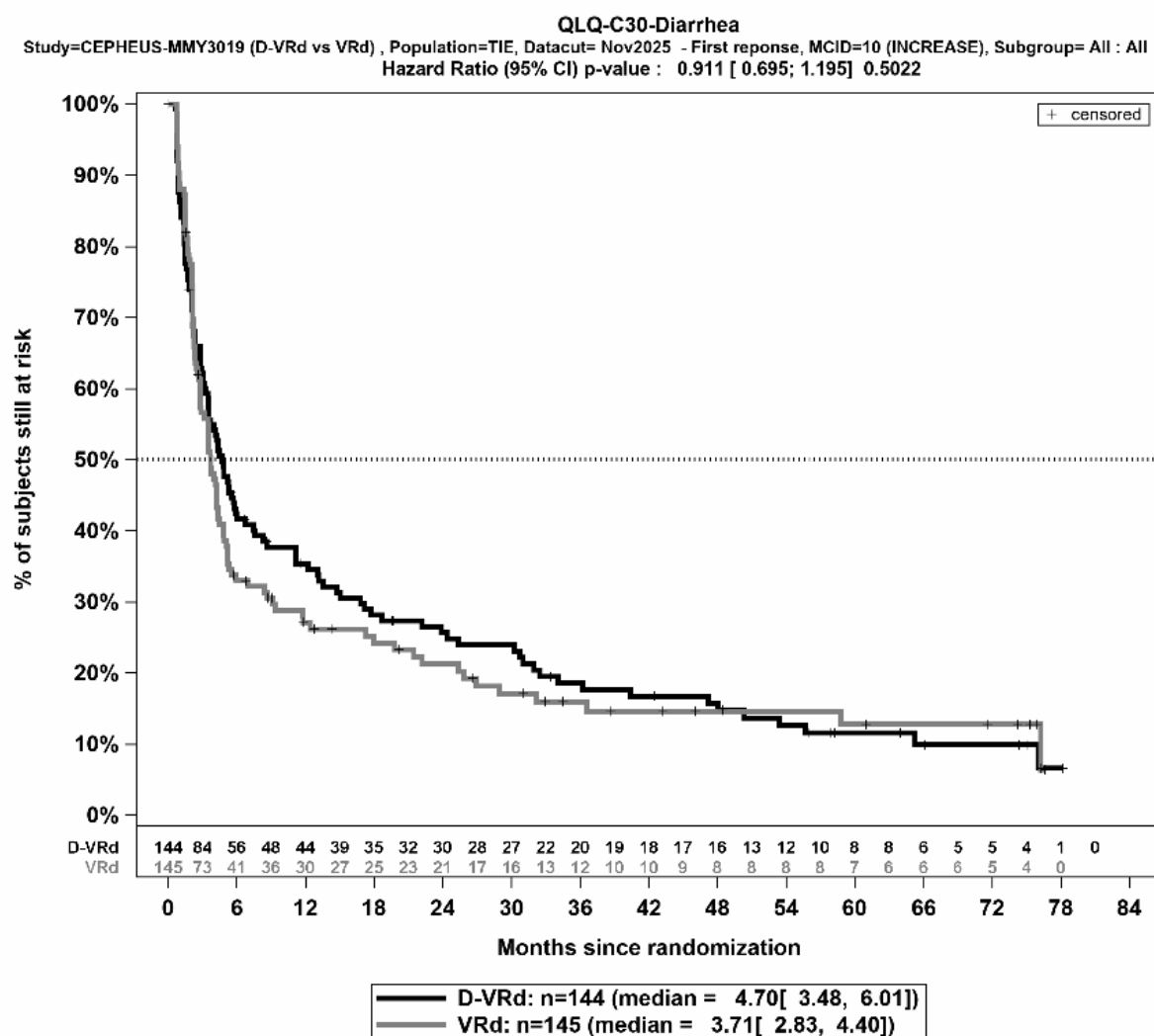


Figure 9: Kaplan-Meier curves for the outcome diarrhoea (EORTC QLQ-C30 – time to first deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025

A.2.2 Symptoms (EORTC QLQ-MY20)

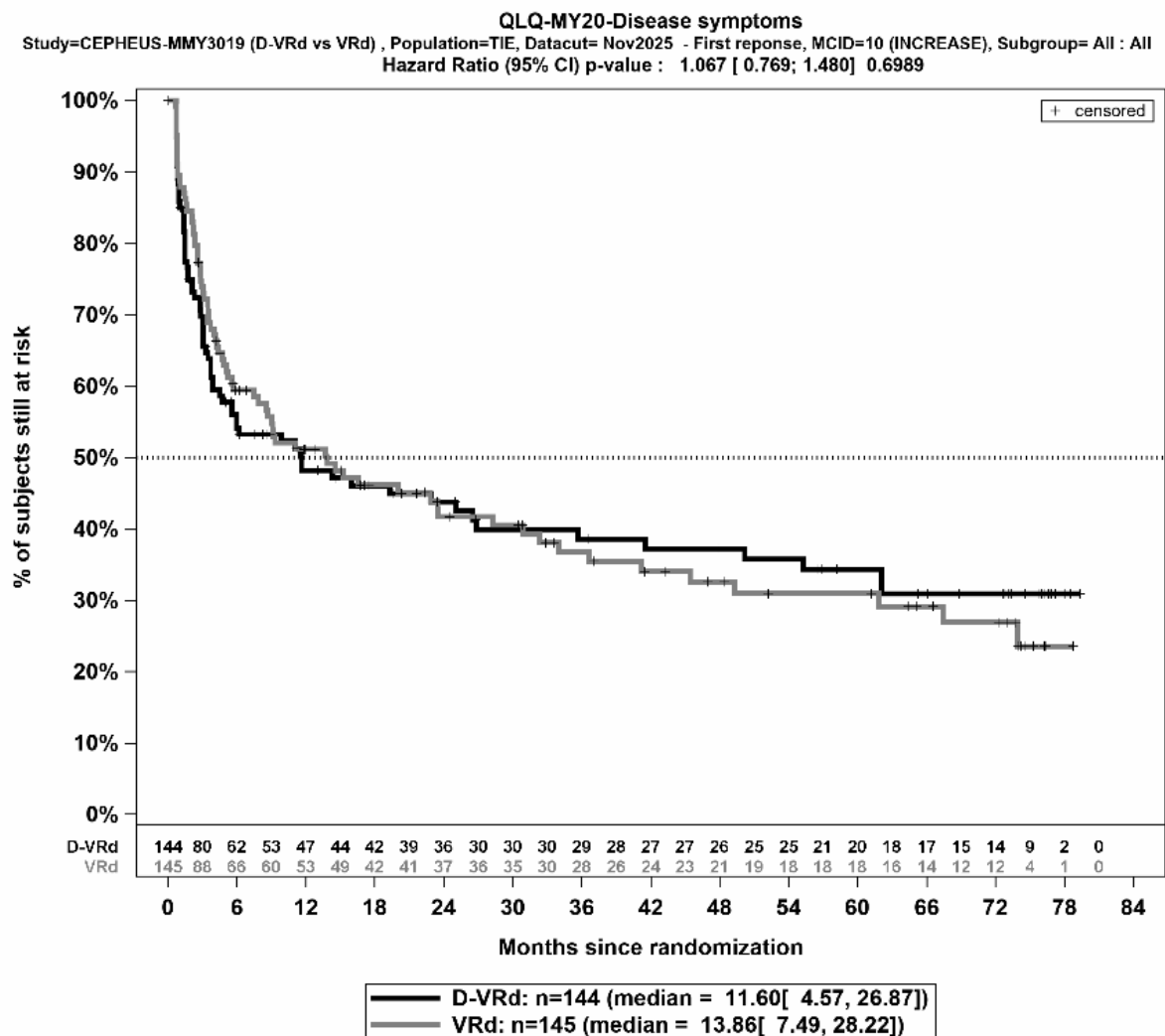


Figure 10: Kaplan-Meier curves for the outcome disease symptoms (EORTC QLQ-MY20 – time to first deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025

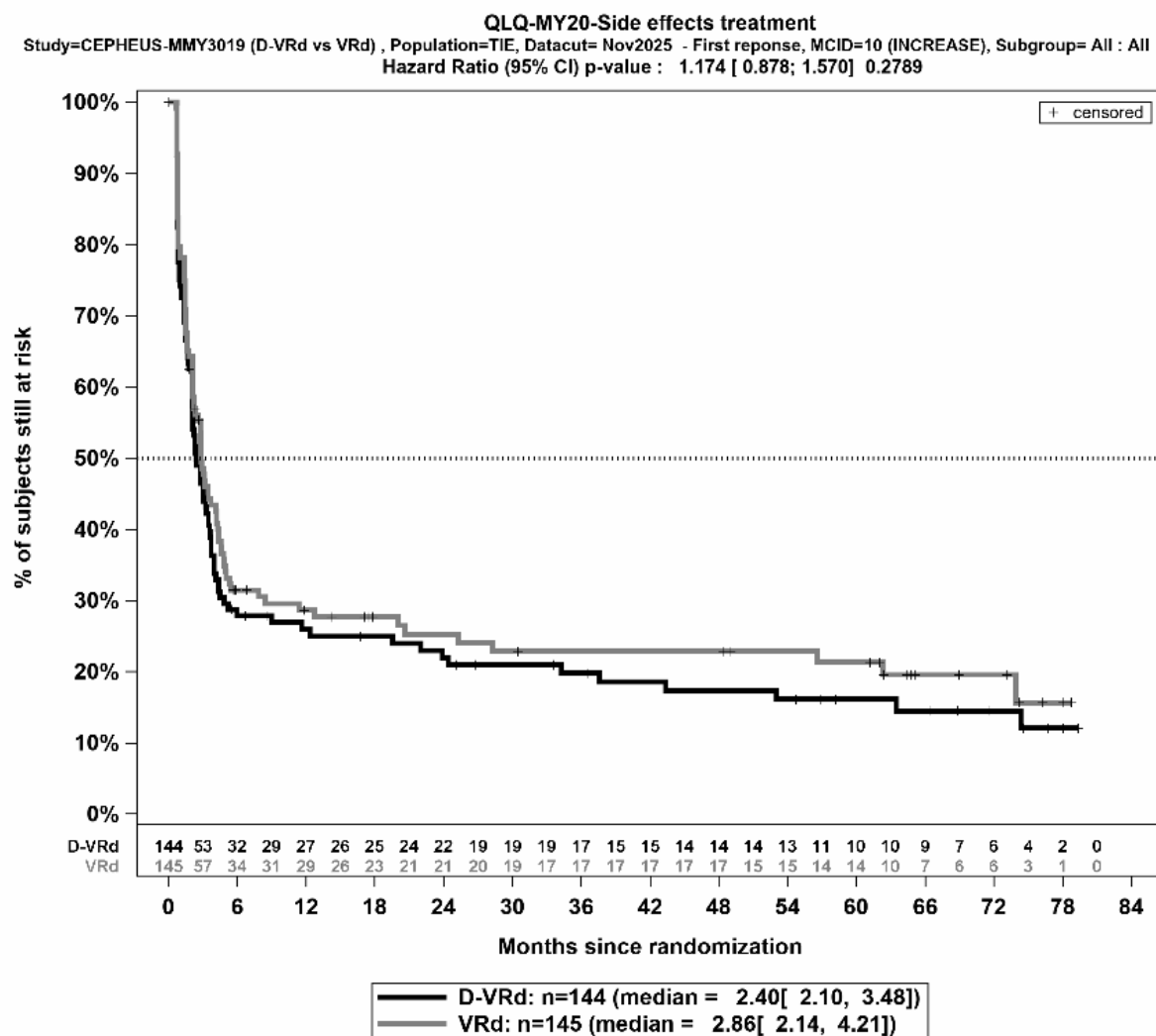


Figure 11: Kaplan-Meier curves for the outcome side effects (EORTC QLQ-MY20 – time to first deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025

A.2.3 Health status (EQ-5D VAS)

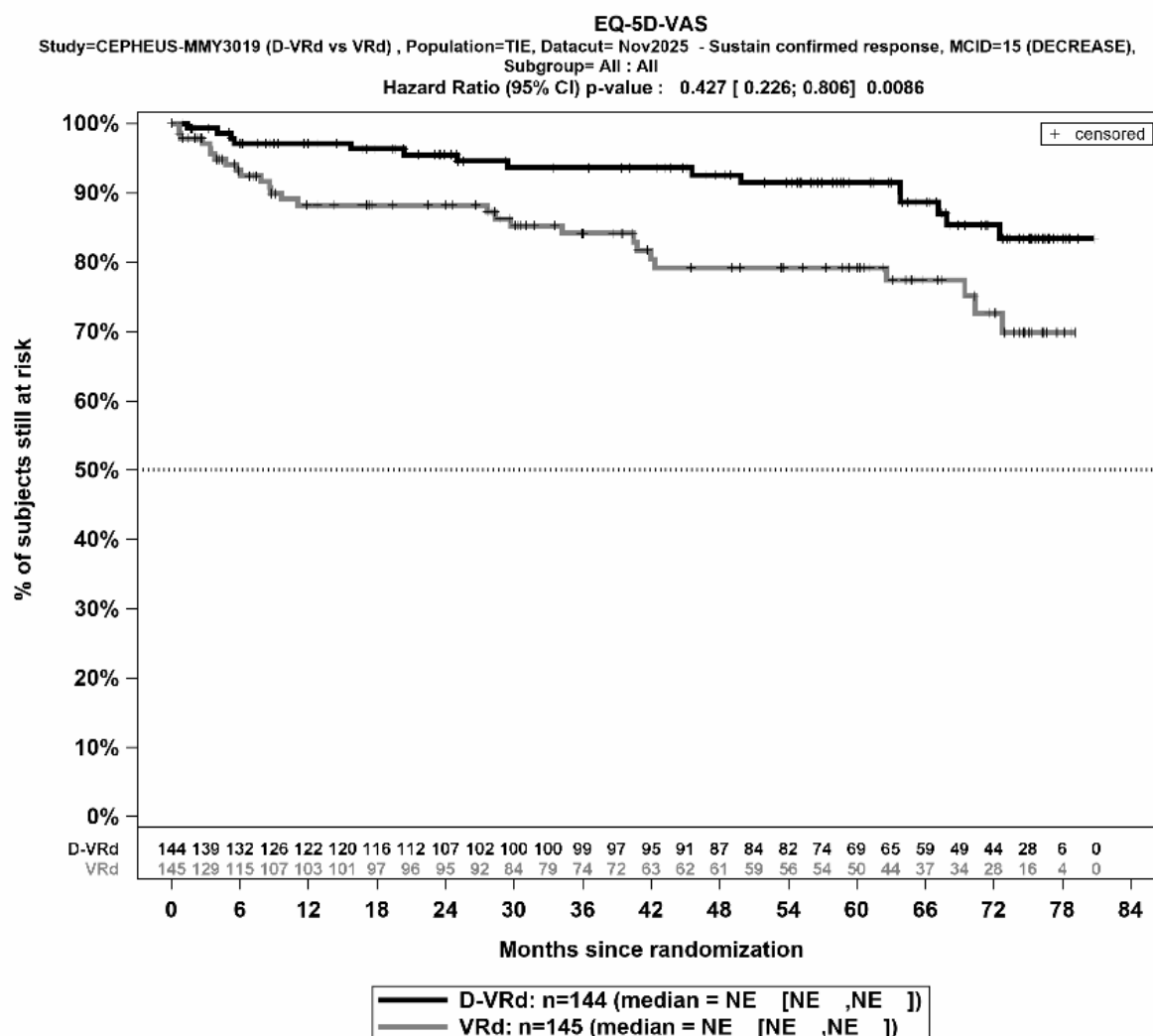


Figure 12: Kaplan-Meier curves for the outcome health status (EQ-5D VAS – time to confirmed permanent deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025

A.3 Health-related quality of life

A.3.1 EORTC QLQ-C30

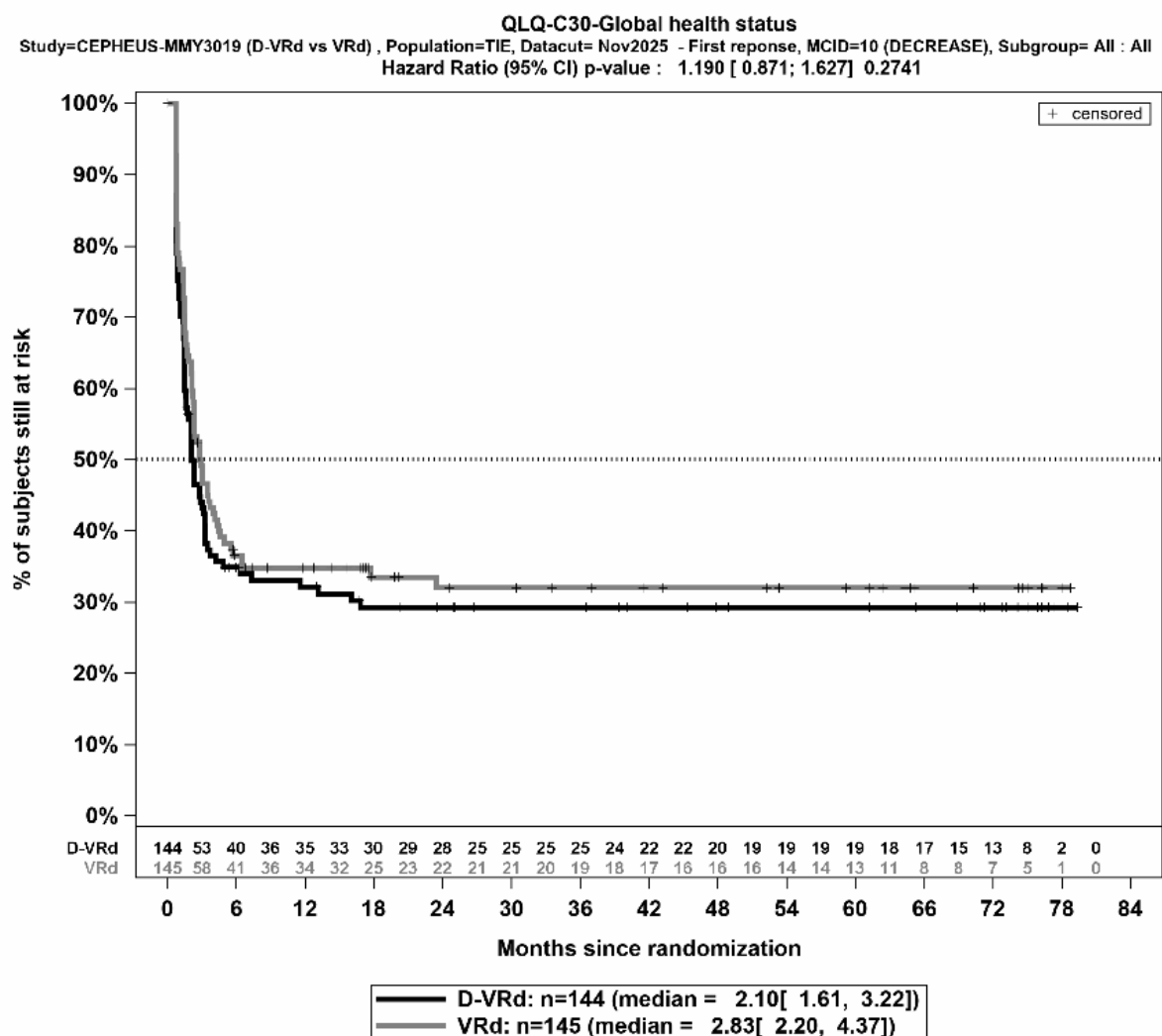


Figure 13: Kaplan-Meier curves for the outcome global health status (EORTC QLQ-C30 – time to first deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025

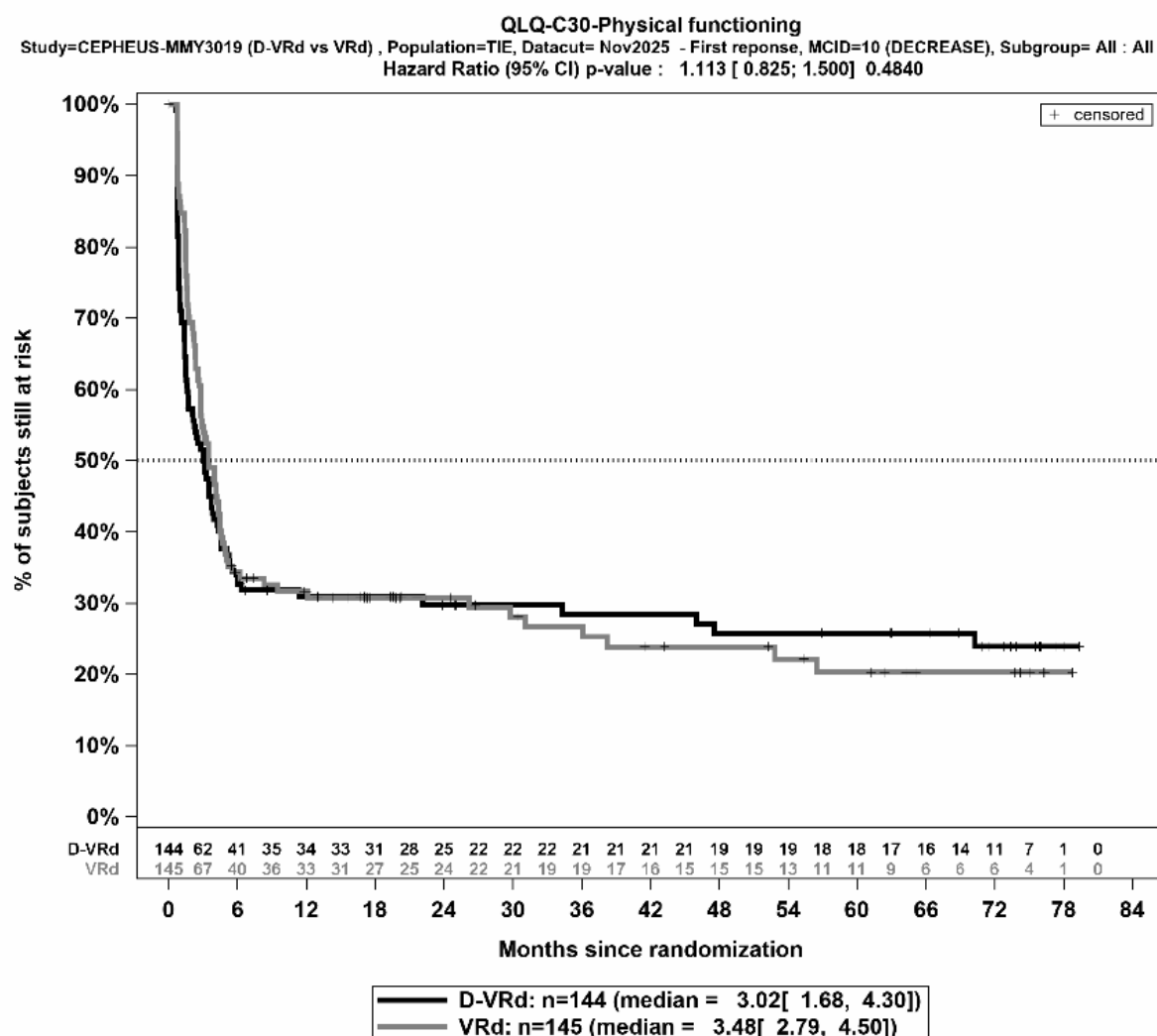


Figure 14: Kaplan-Meier curves for the outcome physical functioning (EORTC QLQ-C30 – time to first deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025

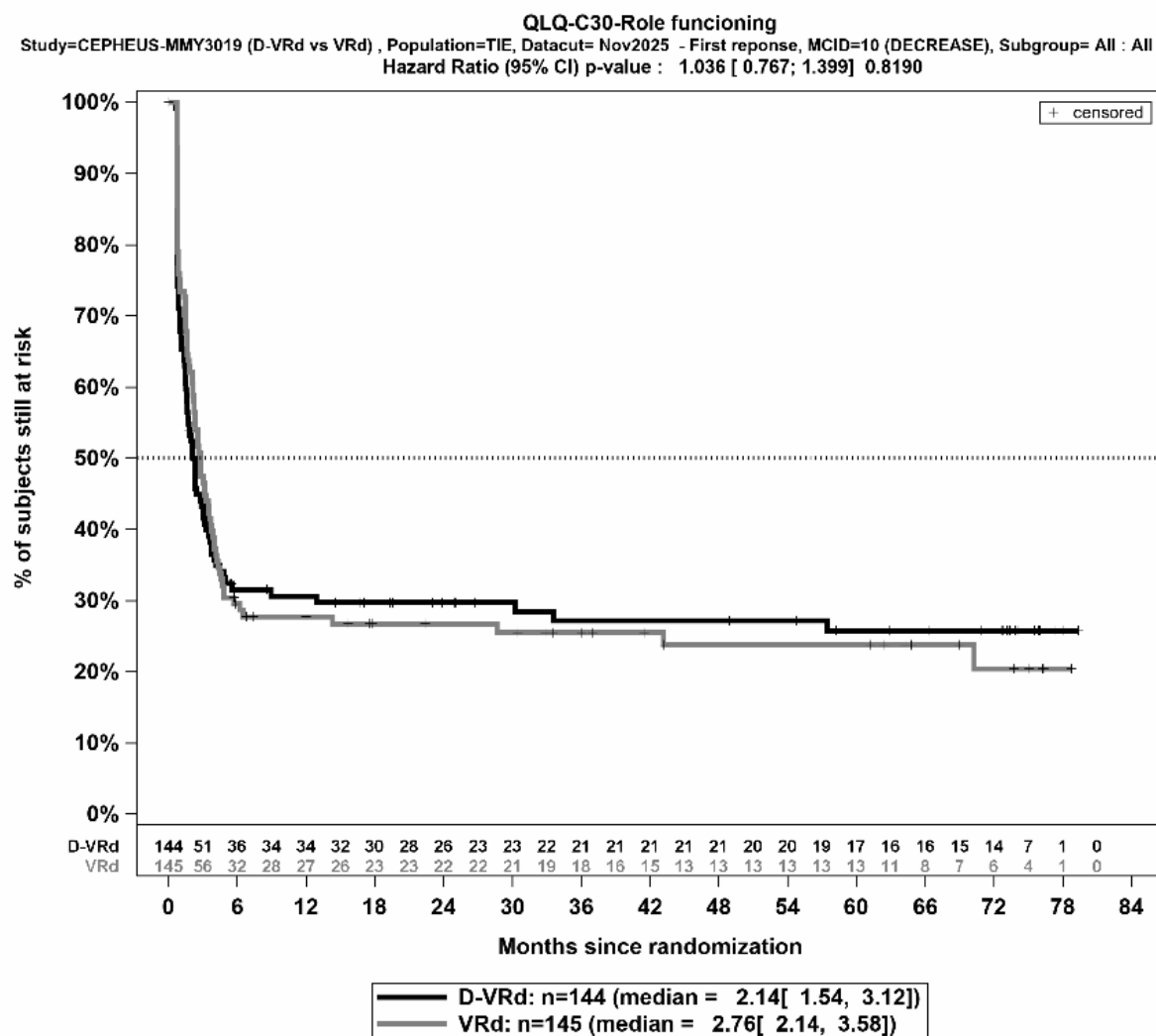


Figure 15: Kaplan-Meier curves for the outcome role functioning (EORTC QLQ-C30 – time to first deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025

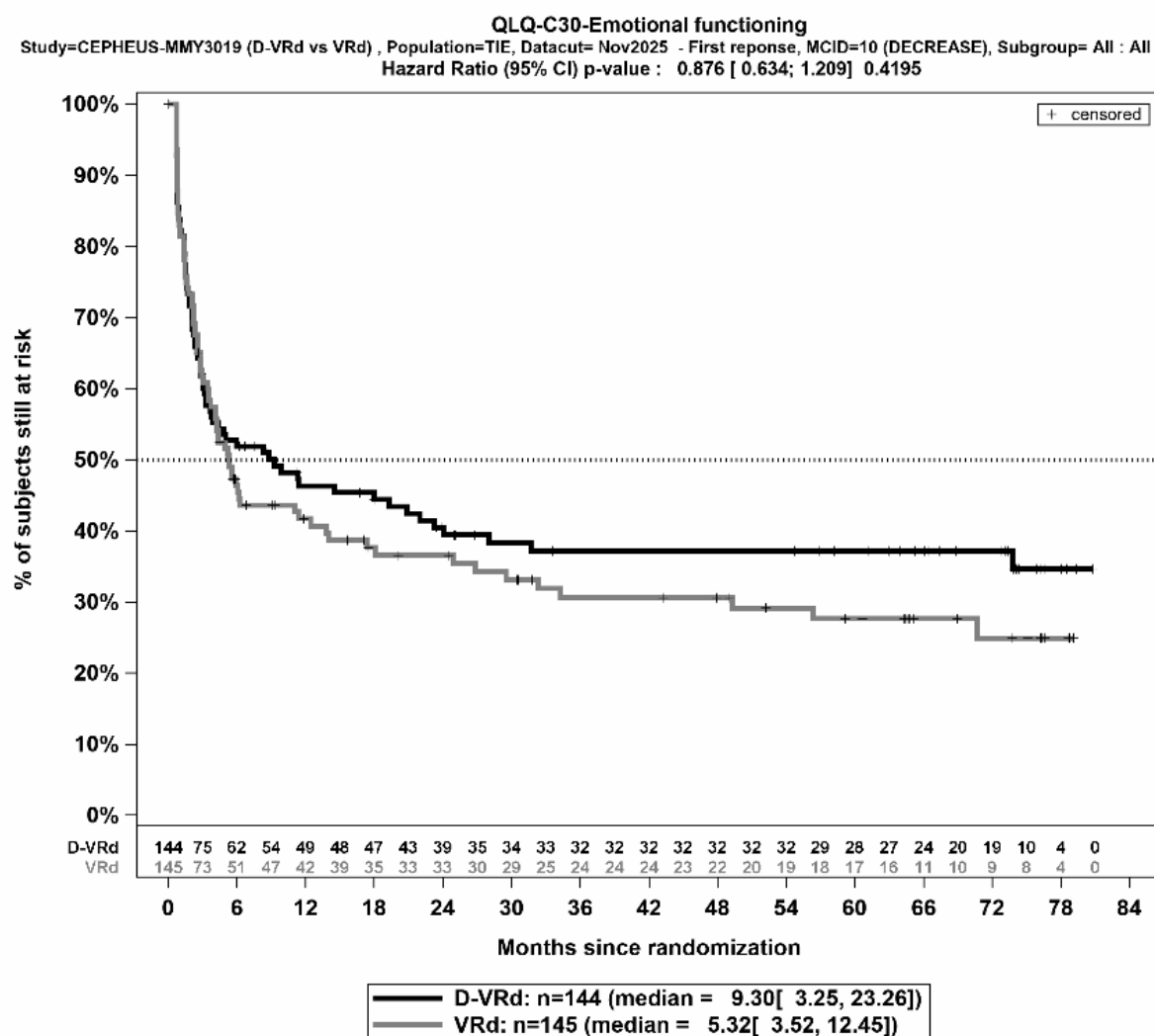


Figure 16: Kaplan-Meier curves for the outcome emotional functioning (EORTC QLQ-C30 – time to first deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025

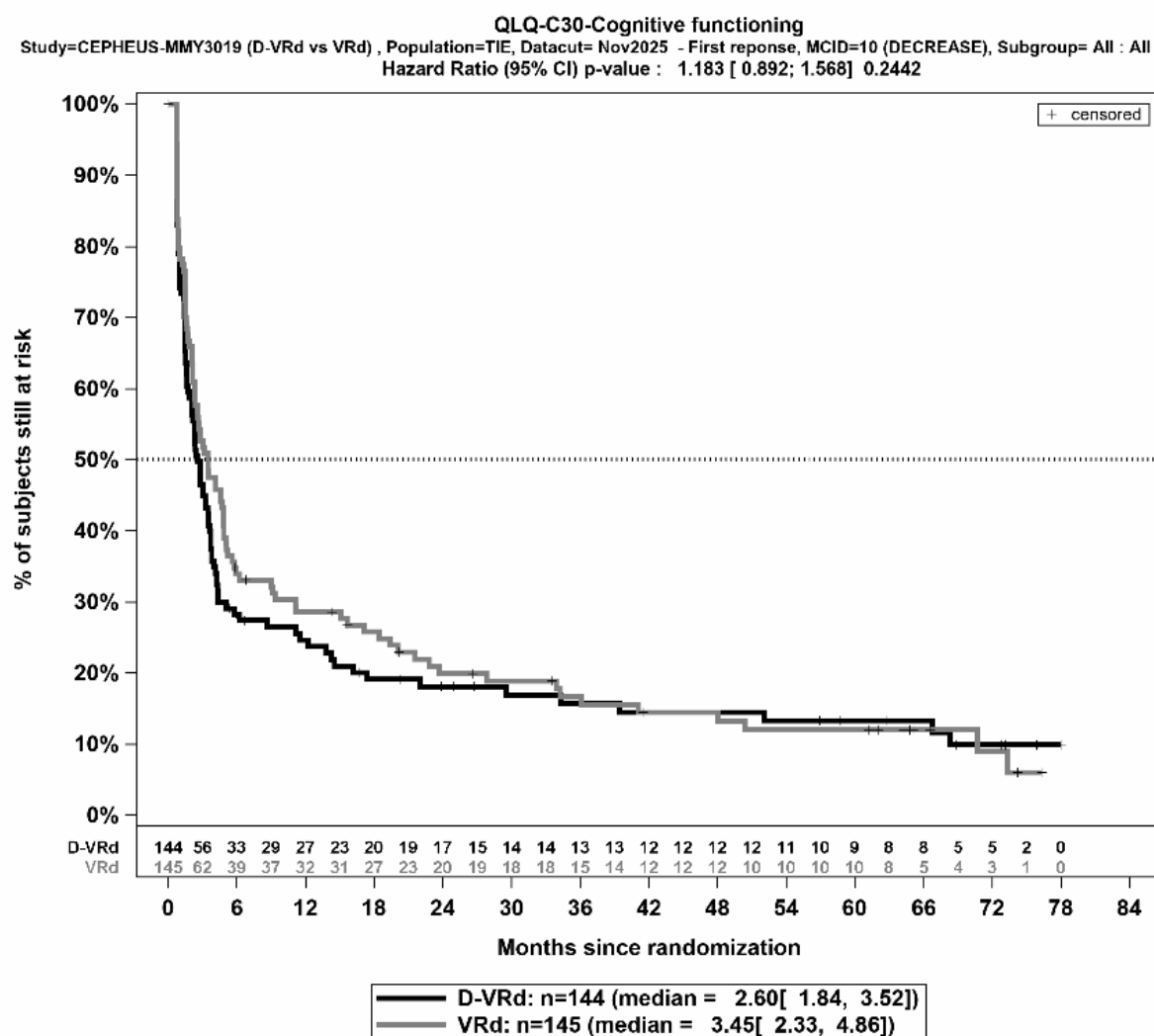


Figure 17: Kaplan-Meier curves for the outcome cognitive functioning (EORTC QLQ-C30 – time to first deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025

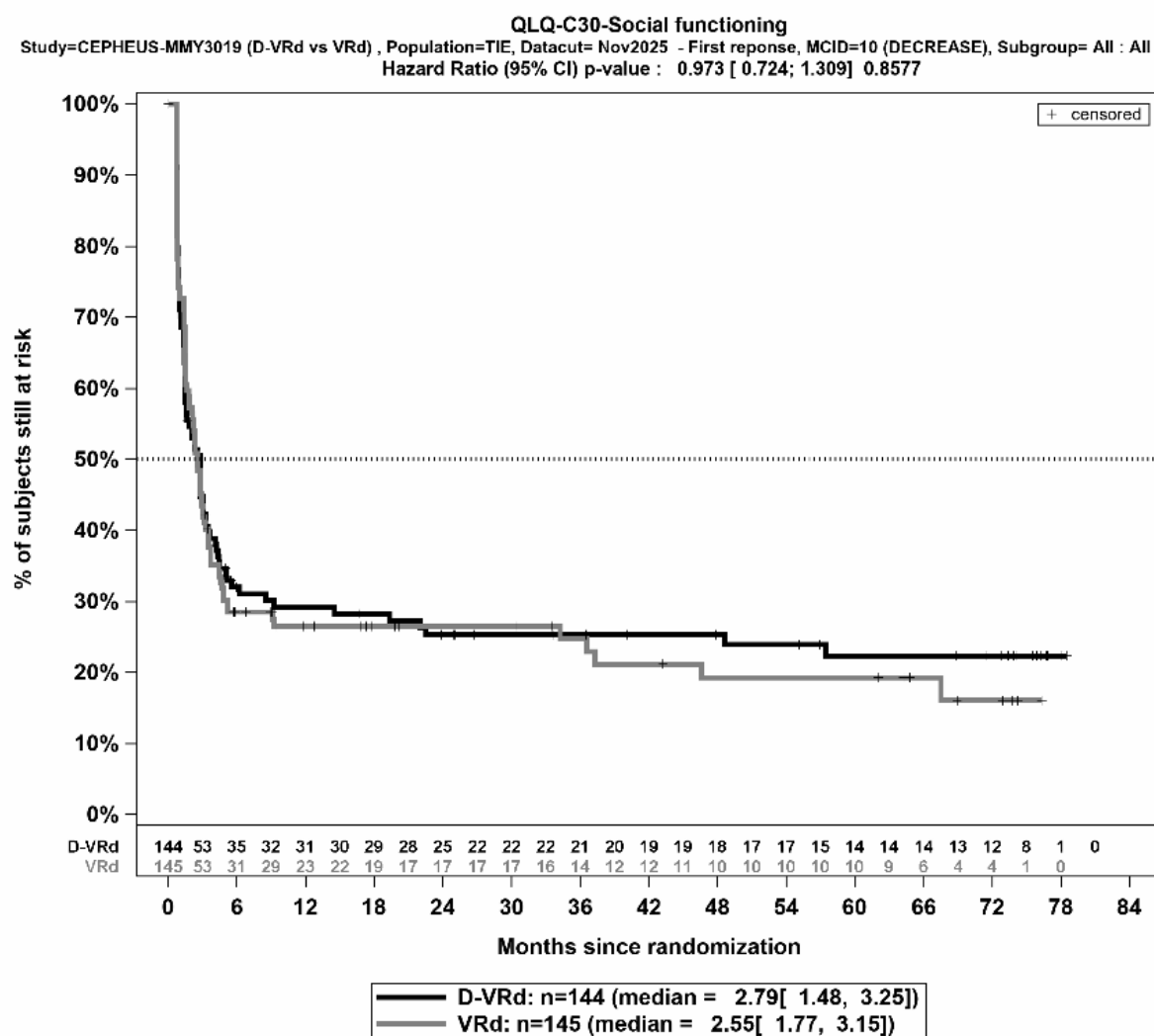


Figure 18: Kaplan-Meier curves for the outcome social functioning (EORTC QLQ-C30 – time to first deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025

A.3.2 EORTC QLQ-MY20

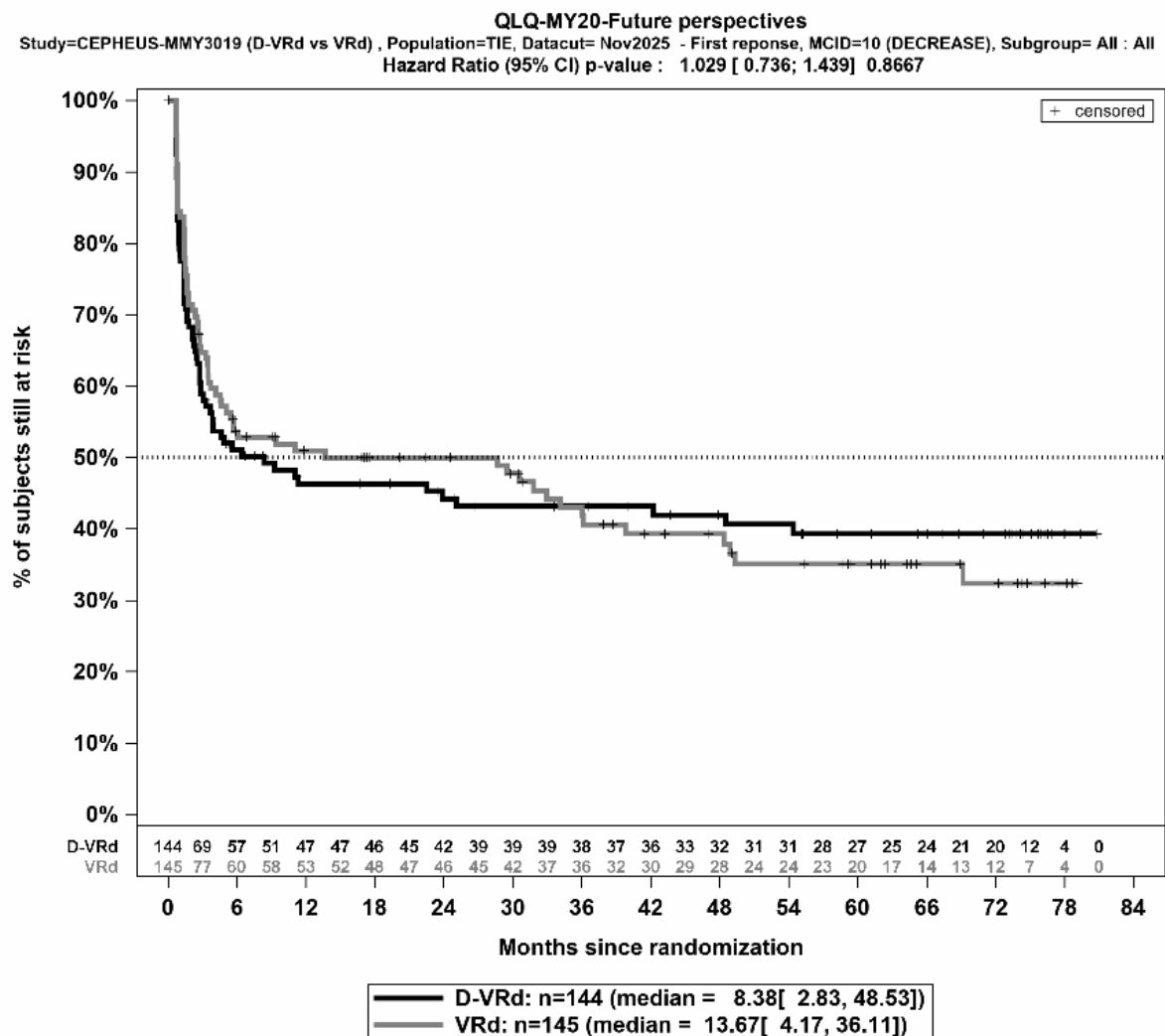


Figure 19: Kaplan-Meier curves for the outcome future perspective (EORTC QLQ-MY20 – time to first deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025

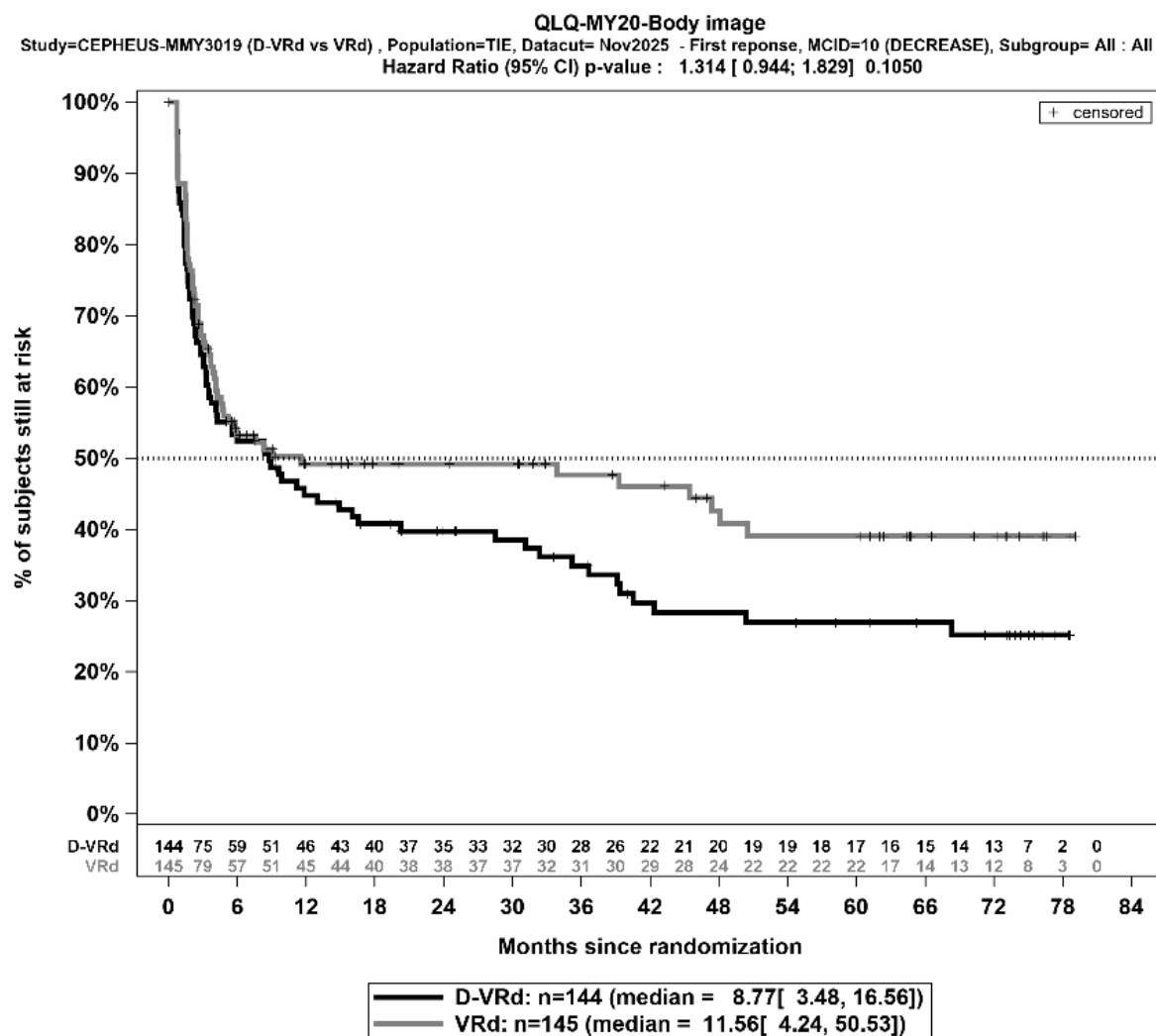


Figure 20: Kaplan-Meier curves for the outcome body image (EORTC QLQ-MY20 – time to first deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025

A.4 Side effects

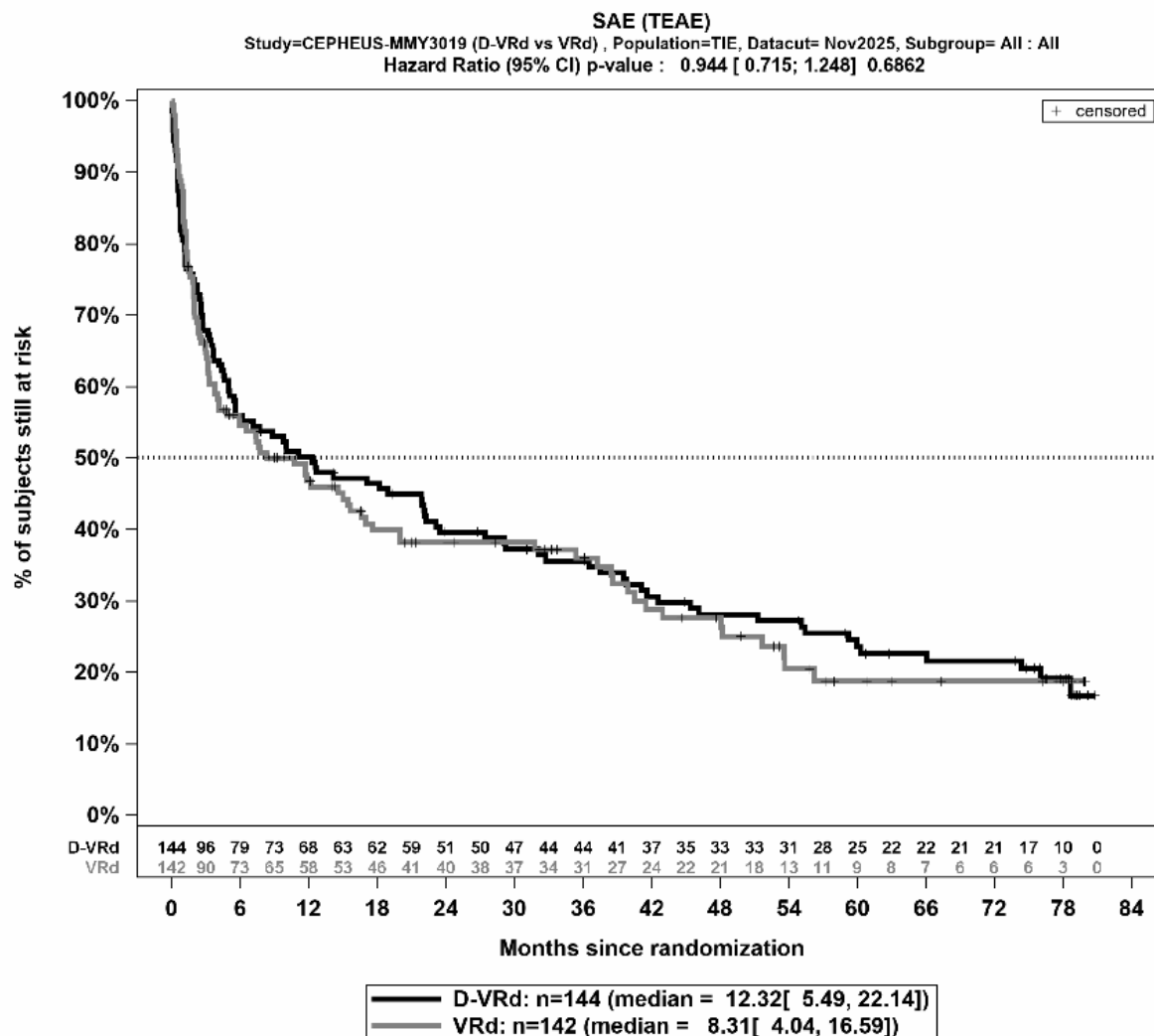


Figure 21: Kaplan-Meier curves for the outcome SAEs, CEPHEUS (relevant subpopulation), data cut from 8 October 2025

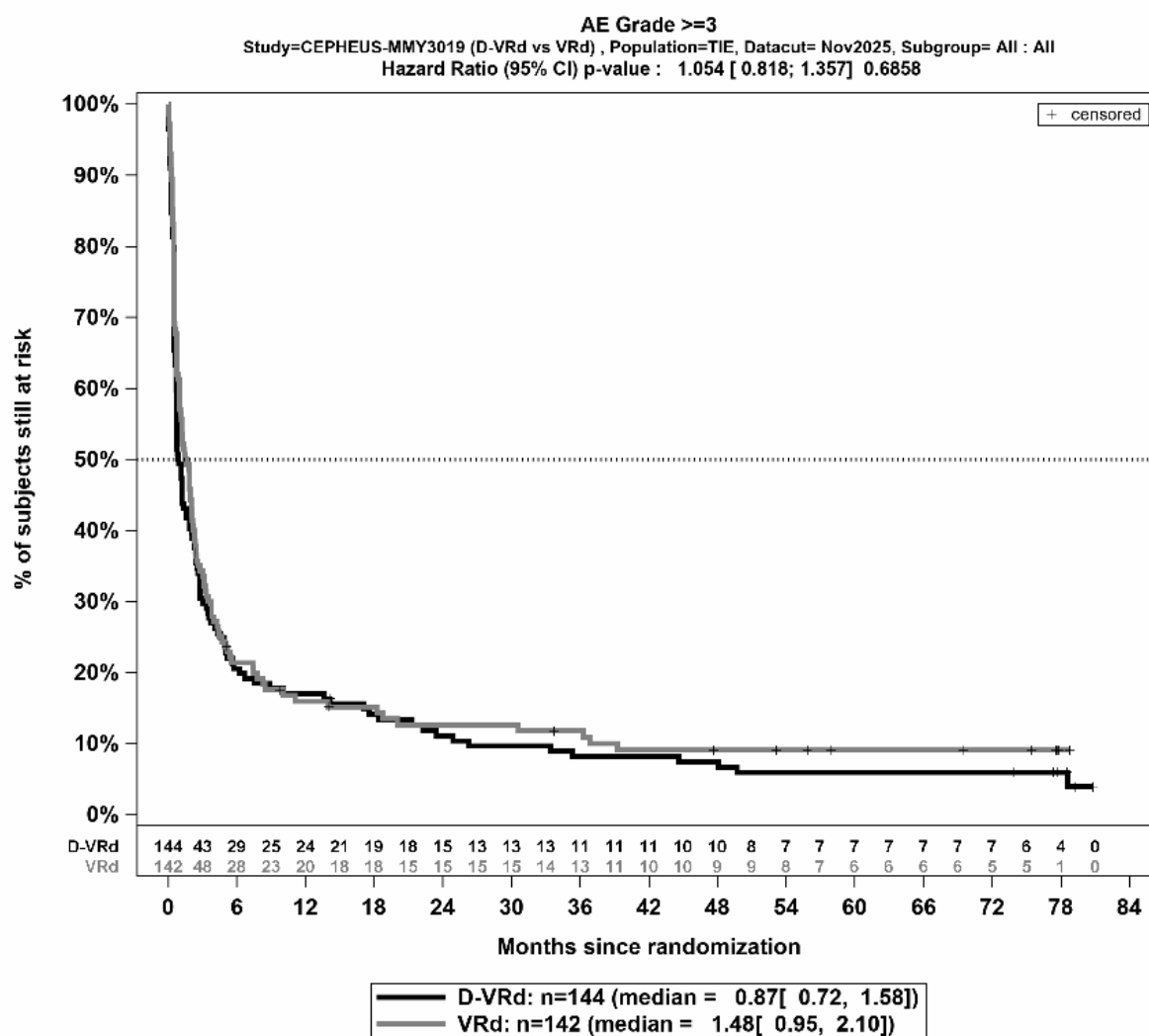


Figure 22: Kaplan-Meier curves for the outcome severe AEs (CTCAE grade ≥ 3), CEPHEUS (relevant subpopulation), data cut from 8 October 2025

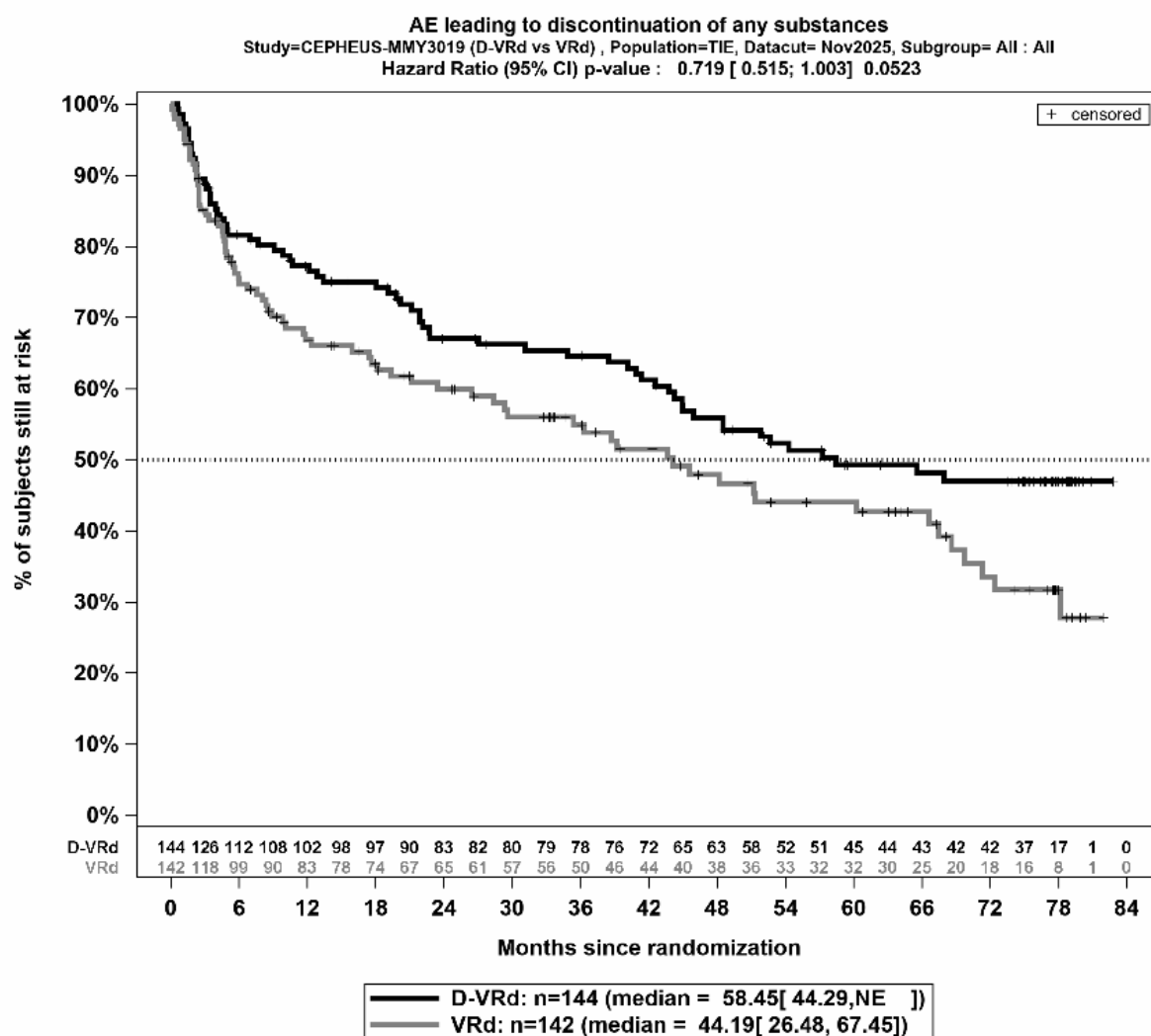


Figure 23: Kaplan-Meier curves for the outcome discontinuation due to AEs (at least one treatment component), CEPHEUS (relevant subpopulation), data cut from 8 October 2025

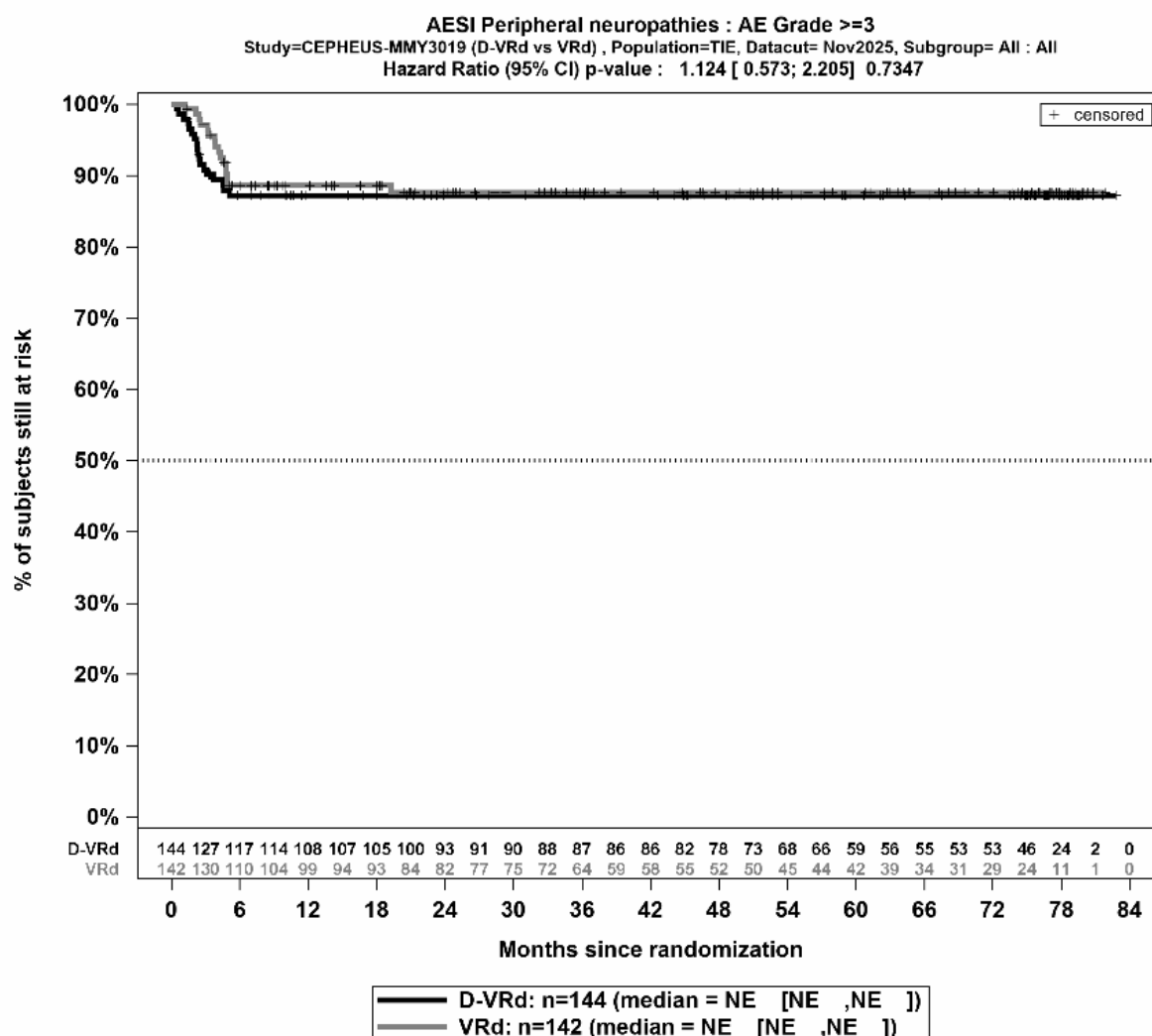


Figure 24: Kaplan-Meier curves for the outcome peripheral neuropathy (HLT, severe AEs [CTCAE grade ≥ 3]), CEPHEUS (relevant subpopulation), data cut from 8 October 2025

Appendix B Results on side effects

For the overall rates of AEs, SAEs, and severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3), the following tables present events for System Organ Classes (SOCs) and Preferred Terms (PTs) according to the Medical Dictionary for Regulatory Activities (MedDRA), each on the basis of the following criteria:

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

For the outcome of discontinuation due to AEs, all events that occurred in ≥ 2 patients in at least one study arm are presented.

Table 8: Common AEs^a – RCT, direct comparison: daratumumab+ bortezomib + lenalidomide + dexamethasone^b vs. bortezomib + lenalidomide + dexamethasone^c, relevant subpopulation (multipage table)

Study SOC ^d PT ^d	Patients with event n (%)	
	daratumumab + bortezomib + lenalidomide + dexamethasone ^b N = 144	bortezomib + lenalidomide + dexamethasone ^c N = 142
CEPHEUS (data cut: 8 October 2025)		
Overall AE rate	144 (100)	142 (100)
Infections and infestations	135 (93.8)	121 (85.2)
COVID-19	54 (37.5)	27 (19.0)
Upper respiratory tract infection	52 (36.1)	38 (26.8)
Pneumonia	41 (28.5)	30 (21.1)
Urinary tract infection	37 (25.7)	27 (19.0)
Nasopharyngitis	26 (18.1)	20 (14.1)
Bronchitis	24 (16.7)	13 (9.2)
Influenza	21 (14.6)	11 (7.7)
Rhinitis	14 (9.7)	7 (4.9)
Conjunctivitis	12 (8.3)	1 (0.7)
Sinusitis	11 (7.6)	3 (2.1)
Tooth infection	11 (7.6)	5 (3.5)
Nervous system disorders	126 (87.5)	117 (82.4)
Peripheral sensory neuropathy	86 (59.7)	9 (64.1)
Dizziness	36 (25.0)	36 (25.4)
Headache	23 (16.0)	14 (9.9)
Neuralgia	18 (12.5)	18 (12.7)
Paraesthesia	17 (11.8)	16 (11.3)
Tremor	16 (11.1)	12 (8.5)
Dysgeusia	13 (9.0)	20 (14.1)
Hypoaesthesia	10 (6.9)	8 (5.6)
Syncope	8 (5.6)	13 (9.2)
Blood and lymphatic system disorders	123 (85.4)	97 (68.3)
Neutropenia	81 (56.3)	60 (42.3)
Thrombocytopenia	70 (48.6)	52 (36.6)
Anaemia	53 (36.8)	47 (33.1)
Lymphopenia	26 (18.1)	19 (13.4)
Leukopenia	16 (11.1)	17 (12.0)
Gastrointestinal disorders	123 (85.4)	116 (81.7)
Diarrhoea	91 (63.2)	88 (62.0)
Constipation	57 (39.6)	66 (46.5)

Table 8: Common AEs^a – RCT, direct comparison: daratumumab+ bortezomib + lenalidomide + dexamethasone^b vs. bortezomib + lenalidomide + dexamethasone^c, relevant subpopulation (multipage table)

Study SOC ^d PT ^d	Patients with event n (%)	
	daratumumab + bortezomib + lenalidomide + dexamethasone ^b N = 144	bortezomib + lenalidomide + dexamethasone ^c N = 142
Nausea	39 (27.1)	36 (25.4)
Abdominal pain	24 (16.7)	16 (11.3)
Vomiting	21 (14.6)	15 (10.6)
Dyspepsia	18 (12.5)	12 (8.5)
Abdominal pain upper	16 (11.1)	9 (6.3)
Stomatitis	11 (7.6)	8 (5.6)
Toothache	11 (7.6)	8 (5.6)
Haemorrhoids	10 (6.9)	6 (4.2)
Gastroesophageal reflux disease	8 (5.6)	10 (7.0)
Abdominal distension	6 (4.2)	10 (7.0)
General disorders and administration site conditions	121 (84.0)	109 (76.8)
Oedema peripheral	63 (43.8)	59 (41.5)
Fatigue	48 (33.3)	55 (38.7)
Asthenia	44 (30.6)	34 (23.9)
Pyrexia	36 (25.0)	25 (17.6)
Injection site erythema	20 (13.9)	7 (4.9)
Influenza like illness	19 (13.2)	17 (12.0)
Peripheral swelling	14 (9.7)	11 (7.7)
Malaise	6 (4.2)	15 (10.6)
Musculoskeletal and connective tissue disorders	110 (76.4)	108 (76.1)
Back pain	44 (30.6)	32 (22.5)
Arthralgia	37 (25.7)	30 (21.1)
Muscle spasms	31 (21.5)	29 (20.4)
Pain in extremity	29 (20.1)	21 (14.8)
Muscular weakness	27 (18.8)	22 (15.5)
Musculoskeletal pain	20 (13.9)	17 (12.0)
Musculoskeletal chest pain	16 (11.1)	11 (7.7)
Bone pain	13 (9.0)	8 (5.6)
Osteoarthritis	10 (6.9)	10 (7.0)
Spinal pain	10 (6.9)	7 (4.9)
Myalgia	10 (6.9)	9 (6.3)

Table 8: Common AEs^a – RCT, direct comparison: daratumumab+ bortezomib + lenalidomide + dexamethasone^b vs. bortezomib + lenalidomide + dexamethasone^c, relevant subpopulation (multipage table)

Study SOC ^d PT ^d	Patients with event n (%)	
	daratumumab + bortezomib + lenalidomide + dexamethasone ^b N = 144	bortezomib + lenalidomide + dexamethasone ^c N = 142
Neck pain	9 (6.3)	11 (7.7)
Metabolism and nutrition disorders	97 (67.4)	81 (57.0)
Hypokalaemia	51 (35.4)	25 (17.6)
Decreased appetite	38 (26.4)	32 (22.5)
Hypocalcaemia	26 (18.1)	16 (11.3)
Hypomagnesaemia	16 (11.1)	12 (8.5)
Hyperglycaemia	14 (9.7)	11 (7.7)
Hyponatraemia	13 (9.0)	17 (12.0)
Hypophosphataemia	11 (7.6)	3 (2.1)
Dehydration	3 (2.1)	11 (7.7)
Respiratory, thoracic and mediastinal disorders	92 (63.9)	69 (48.6)
Cough	40 (27.8)	32 (22.5)
Dyspnoea	30 (20.8)	27 (19.0)
Oropharyngeal pain	13 (9.0)	8 (5.6)
Productive cough	13 (9.0)	7 (4.9)
Rhinorrhoea	11 (7.6)	6 (4.2)
Pulmonary embolism	10 (6.9)	4 (2.8)
Skin and subcutaneous tissue disorders	88 (61.1)	85 (59.9)
Rash	42 (29.2)	36 (25.4)
Dry skin	15 (10.4)	12 (8.5)
Pruritus	14 (9.7)	15 (10.6)
Erythema	11 (7.6)	10 (7.0)
Rash maculo-papular	11 (7.6)	13 (9.2)
Psychiatric disorders	73 (50.7)	71 (50.0)
Insomnia	52 (36.1)	46 (32.4)
Depression	18 (12.5)	11 (7.7)
Anxiety	12 (8.3)	11 (7.7)
Confusional state	9 (6.3)	11 (7.7)
Eye disorders	70 (48.6)	61 (43.0)
Cataract	43 (29.9)	32 (22.5)
Vision blurred	14 (9.7)	16 (11.3)
Dry eye	6 (4.2)	14 (9.9)

Table 8: Common AEs^a – RCT, direct comparison: daratumumab+ bortezomib + lenalidomide + dexamethasone^b vs. bortezomib + lenalidomide + dexamethasone^c, relevant subpopulation (multipage table)

Study SOC ^d PT ^d	Patients with event n (%)	
	daratumumab + bortezomib + lenalidomide + dexamethasone ^b N = 144	bortezomib + lenalidomide + dexamethasone ^c N = 142
Investigations	64 (44.4)	62 (43.7)
Alanine aminotransferase increased	16 (11.1)	18 (12.7)
Blood creatinine increased	11 (7.6)	14 (9.9)
Weight decreased	11 (7.6)	18 (12.7)
Aspartate aminotransferase increased	9 (6.3)	11 (7.7)
Vascular disorders	63 (43.8)	57 (40.1)
Hypotension	23 (16.0)	21 (14.8)
Hypertension	20 (13.9)	12 (8.5)
Deep vein thrombosis	14 (9.7)	12 (8.5)
Haematoma	11 (7.6)	1 (0.7)
Renal and urinary disorders	62 (43.1)	52 (36.6)
Dysuria	15 (10.4)	4 (2.8)
Renal insufficiency	11 (7.6)	18 (12.7)
Injury, poisoning and procedural complications	59 (41.0)	50 (35.2)
Contusion	22 (15.3)	17 (12.0)
Fall	14 (9.7)	12 (8.5)
Cardiac disorders	50 (34.7)	39 (27.5)
Atrial fibrillation	16 (11.1)	17 (12.0)
Ear and labyrinth disorders	32 (22.2)	24 (16.9)
Vertigo	12 (8.3)	10 (7.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	28 (19.4)	26 (18.3)
Reproductive system and breast disorders	21 (14.6)	16 (11.3)
Hepatobiliary disorders	20 (13.9)	18 (12.7)
Immune system disorders	16 (11.1)	6 (4.2)
Hypogammaglobulinaemia	14 (9.7)	2 (1.4)
a. Events that occurred in ≥ 10 patients in at least one study arm. b. Followed by treatment with daratumumab + lenalidomide + dexamethasone in Cycle 9 and beyond. c. Followed by treatment with lenalidomide + dexamethasone in Cycle 9 and beyond. d. MedDRA version 23.0; SOC and PT notation taken without adaptation from Module 4 A and MedDRA. AE: adverse event; COVID-19: coronavirus disease 2019; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; ND: no data; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class		

Table 9: Common SAEs^a – RCT, direct comparison: daratumumab+ bortezomib + lenalidomide + dexamethasone^b vs. bortezomib + lenalidomide + dexamethasone^c, relevant subpopulation

Study SOC ^d PT ^d	Patients with event n (%)	
	daratumumab + bortezomib + lenalidomide + dexamethasone ^b	bortezomib + lenalidomide + dexamethasone ^c
	N = 144	N = 142
CEPHEUS (data cut: 8 October 2025)		
Overall SAE rate	109 (75.7)	99 (69.7)
Infections and infestations	60 (41.7)	47 (33.1)
Pneumonia	23 (16.0)	19 (13.4)
COVID-19	15 (10.4)	6 (4.2)
Cardiac disorders	21 (14.6)	16 (11.3)
Gastrointestinal disorders	19 (13.2)	21 (14.8)
Diarrhoea	11 (7.6)	7 (4.9)
General disorders and administration site conditions	18 (12.5)	12 (8.5)
Musculoskeletal and connective tissue disorders	18 (12.5)	12 (8.5)
Nervous system disorders	16 (11.1)	16 (11.3)
Metabolism and nutrition disorders	14 (9.7)	16 (11.3)
Respiratory, thoracic and mediastinal disorders	14 (9.7)	10 (7.0)
Pulmonary embolism	10 (6.9)	3 (2.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	11 (7.6)	11 (7.7)
Vascular disorders	11 (7.6)	14 (9.9)
Blood and lymphatic system disorders	10 (6.9)	6 (4.2)
Injury, poisoning and procedural complications	9 (6.3)	11 (7.7)
Renal and urinary disorders	8 (5.6)	7 (4.9)
a. Events that occurred in at least one study arm in ≥ 5% of patients. b. Followed by treatment with daratumumab + lenalidomide + dexamethasone in Cycle 9 and beyond. c. Followed by treatment with lenalidomide + dexamethasone in Cycle 9 and beyond. d. MedDRA version 23.0; SOC and PT notation taken without adaptation from Module 4 A. COVID-19: coronavirus disease 2019; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class		

Table 10: Common severe AEs^a (CTCAE grade ≥ 3) – RCT, direct comparison: daratumumab + bortezomib + lenalidomide + dexamethasone^b vs. bortezomib + lenalidomide + dexamethasone^c, relevant subpopulation (multipage table)

Study SOC ^d PT ^d	Patients with event n (%)	
	daratumumab + bortezomib + lenalidomide + dexamethasone ^b N = 144	bortezomib + lenalidomide + dexamethasone ^c N = 142
CEPHEUS (data cut: 8 October 2025)		
Overall rate of severe AEs (CTCAE grade ≥ 3)	135 (93.8)	126 (88.7)
Blood and lymphatic system disorders	94 (65.3)	77 (54.2)
Neutropenia	65 (45.1)	47 (33.1)
Thrombocytopenia	44 (30.6)	33 (23.2)
Anaemia	20 (13.9)	21 (14.8)
Lymphopenia	16 (11.1)	14 (9.9)
Infections and infestations	63 (43.8)	47 (33.1)
Pneumonia	26 (18.1)	19 (13.4)
COVID-19	14 (9.7)	5 (3.5)
Urinary tract infection	8 (5.6)	4 (2.8)
Metabolism and nutrition disorders	37 (25.7)	32 (22.5)
Hypokalaemia	22 (15.3)	13 (9.2)
Hyponatraemia	6 (4.2)	8 (5.6)
Nervous system disorders	37 (25.7)	33 (23.2)
Peripheral sensory neuropathy	14 (9.7)	12 (8.5)
Syncope	7 (4.9)	9 (6.3)
General disorders and administration site conditions	34 (23.6)	26 (18.3)
Fatigue	13 (9.0)	15 (10.6)
Musculoskeletal and connective tissue disorders	32 (22.2)	24 (16.9)
Muscular weakness	10 (6.9)	8 (5.6)
Gastrointestinal disorders	30 (20.8)	30 (21.1)
Diarrhoea	20 (13.9)	15 (10.6)
Cardiac disorders	22 (15.3)	19 (13.4)
Respiratory, thoracic and mediastinal disorders	22 (15.3)	11 (7.7)
Pulmonary embolism	10 (6.9)	4 (2.8)
Vascular disorders	21 (14.6)	17 (12.0)
Hypertension	10 (6.9)	3 (2.1)
Eye disorders	17 (11.8)	14 (9.9)
Cataract	14 (9.7)	10 (7.0)

Table 10: Common severe AEs^a (CTCAE grade ≥ 3) – RCT, direct comparison: daratumumab+ bortezomib + lenalidomide + dexamethasone^b vs. bortezomib + lenalidomide + dexamethasone^c, relevant subpopulation (multipage table)

Study SOC ^d PT ^d	Patients with event n (%)	
	daratumumab + bortezomib + lenalidomide + dexamethasone ^b N = 144	bortezomib + lenalidomide + dexamethasone ^c N = 142
Investigations	14 (9.7)	11 (7.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	14 (9.7)	11 (7.7)
Renal and urinary disorders	14 (9.7)	15 (10.6)
Skin and subcutaneous tissue disorders	13 (9.0)	9 (6.3)
Psychiatric disorders	10 (6.9)	7 (4.9)
Injury, poisoning and procedural complications	6 (4.2)	10 (7.0)
a. Events that occurred in at least one study arm in $\geq 5\%$ of patients. b. Followed by treatment with daratumumab + lenalidomide + dexamethasone in Cycle 9 and beyond. c. Followed by treatment with lenalidomide + dexamethasone in Cycle 9 and beyond. d. MedDRA version 23.0; SOC and PT notation taken without adaptation from Module 4 A and MedDRA. AE: adverse event; COVID-19: coronavirus disease 2019; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class		

Table 11: Common discontinuations due to AEs^a (at least one treatment component) – RCT, direct comparison: daratumumab+ bortezomib + lenalidomide + dexamethasone^b vs. bortezomib + lenalidomide + dexamethasone^c, relevant subpopulation (multipage table)

Study SOC ^d PT ^d	Patients with event n (%)	
	daratumumab + bortezomib + lenalidomide + dexamethasone N = 144	bortezomib + lenalidomide + dexamethasone N = 142
CEPHEUS (data cut: 8 October 2025)		
Overall rate of discontinuations due to AEs (at least one treatment component)	67 (46.5)	75 (52.8)
Nervous system disorders	21 (14.6)	24 (16.9)
Peripheral sensory neuropathy	12 (8.3)	14 (9.9)
Peripheral sensorimotor neuropathy	2 (1.4)	2 (1.4)
Dementia	2 (1.4)	0 (0.0)
Dementia Alzheimer's type	2 (1.4)	0 (0.0)
Neuralgia	2 (1.4)	3 (2.1)
Tremor	0 (0.0)	2 (1.4)
Infections and infestations	13 (9.0)	9 (6.3)
COVID-19	4 (2.8)	1 (0.7)
Pneumonia	3 (2.1)	2 (1.4)
COVID-19 pneumonia	2 (1.4)	1 (0.7)
General disorders and administration site conditions	7 (4.9)	14 (9.9)
General physical health deterioration	3 (2.1)	1 (0.7)
Asthenia	1 (0.7)	2 (1.4)
Fatigue	1 (0.7)	4 (2.8)
Oedema peripheral	0 (0.0)	4 (2.8)
Peripheral swelling	0 (0.0)	2 (1.4)
Psychiatric disorders	7 (4.9)	10 (7.0)
Insomnia	5 (3.5)	3 (2.1)
Affective disorder	0 (0.0)	2 (1.4)
Gastrointestinal disorders	6 (4.2)	9 (6.3)
Diarrhoea	5 (3.5)	7 (4.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6 (4.2)	10 (7.0)
Prostate cancer	0 (0.0)	3 (2.1)
Skin and subcutaneous tissue disorders	6 (4.2)	6 (4.2)
Rash	3 (2.1)	2 (1.4)
Cardiac disorders	4 (2.8)	3 (2.1)
Cardiac arrest	2 (1.4)	1 (0.7)

Table 11: Common discontinuations due to AEs^a (at least one treatment component) – RCT, direct comparison: daratumumab+ bortezomib + lenalidomide + dexamethasone^b vs. bortezomib + lenalidomide + dexamethasone^c, relevant subpopulation (multipage table)

Study SOC ^d PT ^d	Patients with event n (%)	
	daratumumab + bortezomib + lenalidomide + dexamethasone N = 144	bortezomib + lenalidomide + dexamethasone N = 142
Musculoskeletal and connective tissue disorders	3 (2.1)	8 (5.6)
Muscular weakness	2 (1.4)	5 (3.5)
Respiratory, thoracic and mediastinal disorders	3 (2.1)	0 (0.0)
Pulmonary embolism	3 (2.1)	0 (0.0)
Blood and lymphatic system disorders	2 (1.4)	1 (0.7)
Eye disorders	2 (1.4)	2 (1.4)
Metabolism and nutrition disorders	2 (1.4)	5 (3.5)
Hypokalaemia	0 (0.0)	2 (1.4)
Vascular disorders	0 (0.0)	4 (2.8)
Orthostatic hypotension	0 (0.0)	2 (1.4)
a. Events that occurred in ≥ 2 patients in at least one study arm. b. Followed by treatment with daratumumab + lenalidomide + dexamethasone in Cycle 9 and beyond. c. Followed by treatment with lenalidomide + dexamethasone in Cycle 9 and beyond. d. MedDRA version 23.0; SOC and PT notation taken without adaptation from Module 4 A and MedDRA. AE: adverse event; COVID-19: coronavirus disease 2019; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; ND: no data; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class		

Appendix C Supplementary information on health status (EQ-5D VAS)

C.1 Results

Table 12: Results on health status (EQ-5D VAS) presented as supplementary information – RCT, direct comparison: daratumumab+ bortezomib + lenalidomide + dexamethasone^a vs. bortezomib + lenalidomide + dexamethasone^b, relevant subpopulation

Study Outcome category Outcome	daratumumab + bortezomib + lenalidomide + dexamethasone ^a		bortezomib + lenalidomide + dexamethasone ^b		daratumumab + bortezomib + lenalidomide + dexamethasone ^a vs. bortezomib + lenalidomide + dexamethasone ^b HR [95% CI]; p-value ^c
	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 (%)	
CEPHEUS (data cut: 8 October 2025)					
Morbidity					
Health status (EQ-5D VAS)					
Time to first deterioration ^{d, e}	121	4.2 [3.0; 18.7] 72 (59.5 ^f)	125	5.7 [3.5; 38.7] 72 (57.6 ^f)	1.12 [0.80; 1.57]; 0.507
Time to confirmed deterioration ^{d, e}	121	NA 43 (35.5 ^f)	125	NA [56.6; NA] 52 (41.6 ^f)	0.71 [0.47; 1.07]; 0.100
a. Followed by treatment with daratumumab + lenalidomide + dexamethasone in Cycle 9 and beyond. b. Followed by treatment with lenalidomide + dexamethasone in Cycle 9 and beyond. c. Effect, CI and p-value according to information provided by the company: Cox proportional hazards model; each stratified according to ISS stage (I vs. II vs. III) and age/ASCT eligibility (≥ 70 years vs. < 70 years ASCT ineligible vs. < 70 years and refusal to have ASCT). Patients < 70 years who had refused ASCT were not included in the subpopulation relevant for the benefit assessment, which was analysed here. d. According to Module 4 A, only patients with a baseline value and at least one other value in the course of the study are included in the analyses. e. An EQ-5D VAS score decrease by ≥ 15 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100). f. Institute’s calculation. ASCT: autologous stem cell transplantation; CI: confidence interval; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; RCT: randomized controlled trial; VAS: visual analogue scale					

C.2 Kaplan-Meier curves

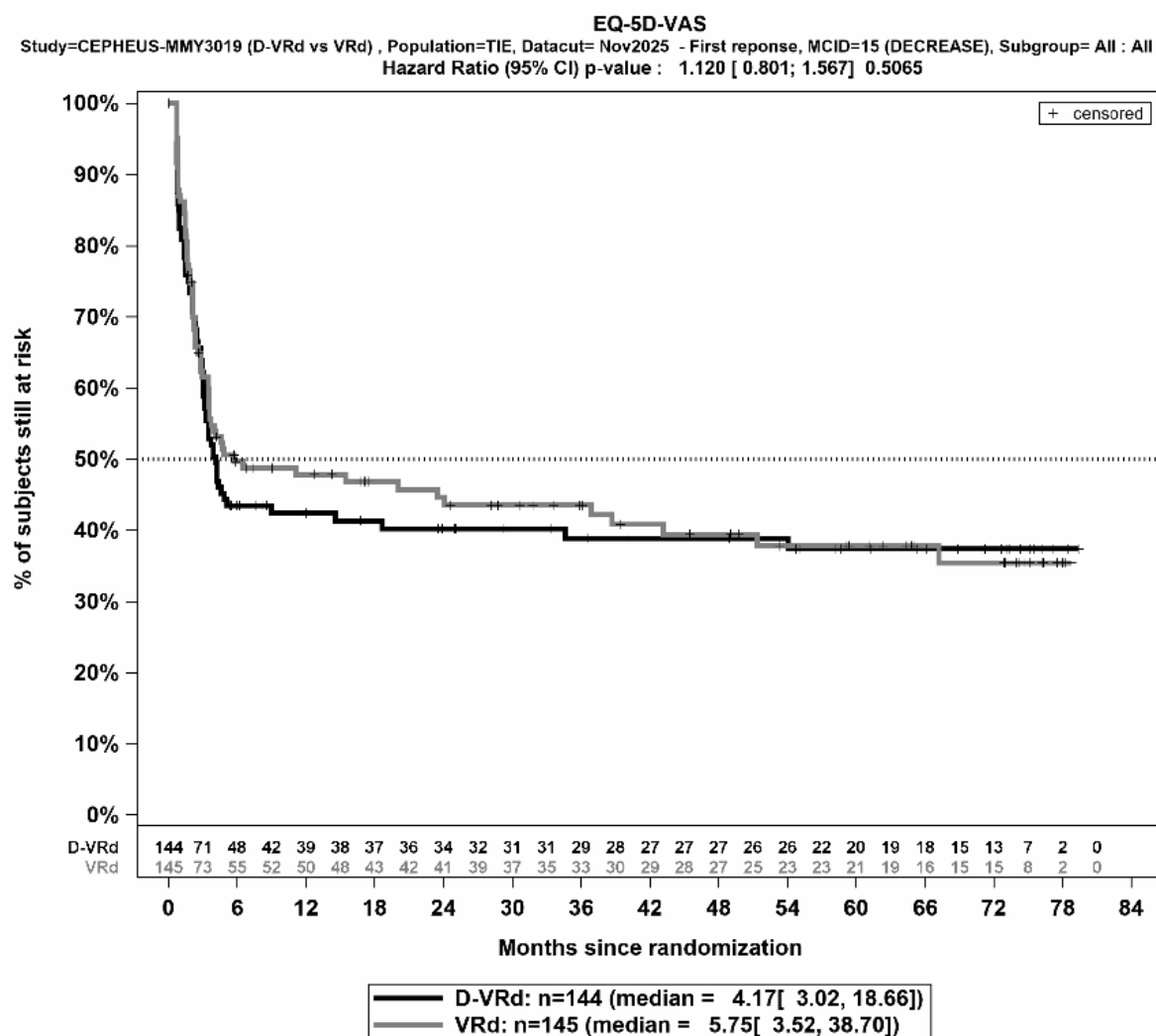


Figure 25: Kaplan-Meier curves for the outcome health status (EQ-5D VAS – time to first deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025

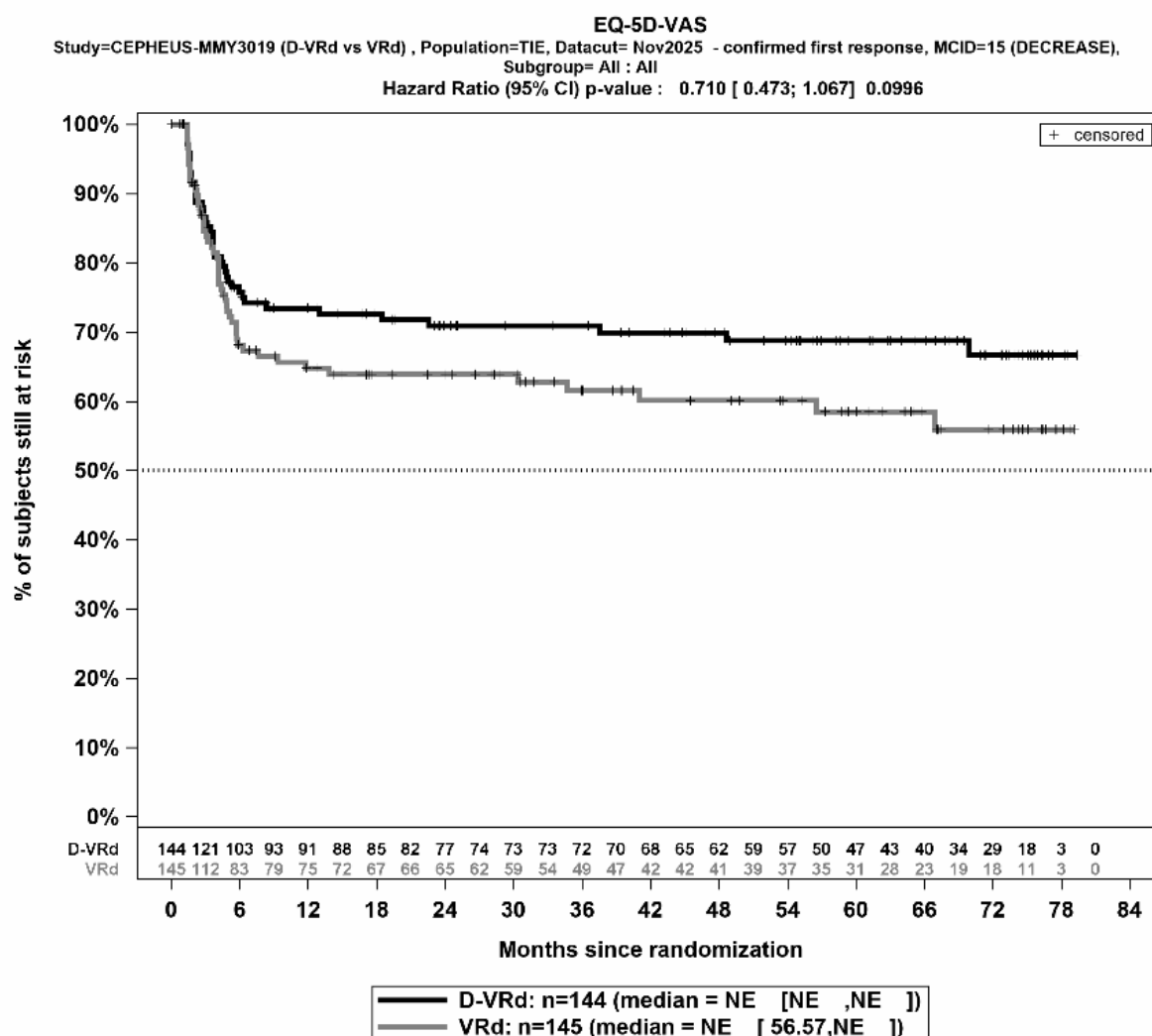


Figure 26: Kaplan-Meier curves for the outcome health status (EQ-5D VAS – time to confirmed deterioration), CEPHEUS (relevant subpopulation), data cut from 8 October 2025