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Daratumumab (newly diagnosed multiple myeloma, stem cell transplant suitable) –

Addendum to Commission A20-15[1]

Addendum

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Table of contents

List of tables

Page

List of figures

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ASCT	autologous stem cell transplantation
CTCAE	Common Terminology Criteria for Adverse Events
D-VTd	daratumumab + bortezomib + thalidomide + dexamethasone
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ISS	International Staging System
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire-Core 30
SAE	serious adverse event
SOC	System Organ Class
VAS	visual analogue scale
VTd	bortezomib + thalidomide + dexamethasone

1 Background

On 23 June 2020, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A20-15 (Daratumumab – Benefit assessment according to §35a Social Code Book V) [1].

The research question of the benefit assessment is to assess the added benefit of daratumumab in combination with bortezomib, thalidomide and dexamethasone (D-VTd) in comparison with the appropriate comparator therapy (ACT) in adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplantation (ASCT).

For this purpose, the pharmaceutical company (hereinafter referred to as "the company") presented the CASSIOPEIA study in its dossier [2]. The dossier assessment concluded that the CASSIOPEIA study was unsuitable for the assessment of the added benefit of daratumumab in the therapeutic indication to be assessed [1]. This is due to the fact that the ACT specified by the G-BA (consisting of induction therapy, ASCT and maintenance therapy) was not implemented in the CASSIOPEIA study.

The G-BA commissioned IQWiG with the assessment of the data of Part 1 of the CASSIOPEIA study (first and second data cut-off) presented in the dossier under consideration of the information from the commenting procedure [3].

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

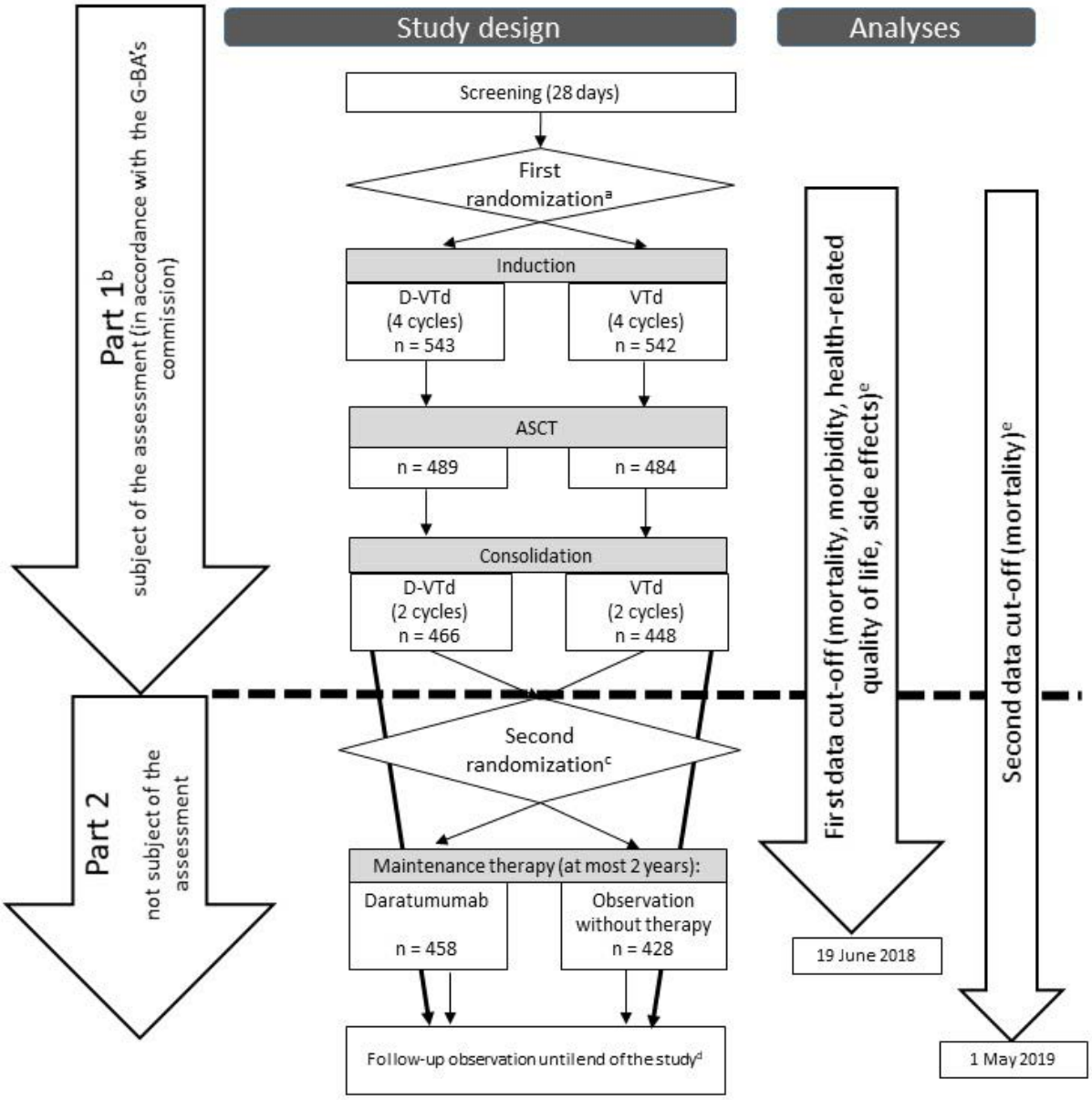
2.1 CASSIOPEIA study

The subject of the present assessment is the CASSIOPEIA study (Part 1) [4-8]. Detailed characteristics of the CASSIOPEIA study, including information on the study design and the interventions used, can be found in benefit assessment A20-15 [1].

The CASSIOPEIA study is an open-label, randomized, actively controlled study comparing D-VTd with a combination of bortezomib, thalidomide and dexamethasone (VTd). The study included adult patients with newly diagnosed multiple myeloma who were eligible for high dose therapy and ASCT and not older than 65 years of age.

In total, 1085 patients were randomized in a 1:1 ratio and allocated to the 2 treatment arms: 543 patients to the D-VTd arm and 542 patients to the VTd arm.

Figure 1 presents a schematic diagram of the study design of the CASSIOPEIA study.



a. The first patient was randomized to the study on 22 September 2015.
b. The median treatment duration is 8.9 months in the D-VTd arm and 8.7 months in the VTd arm.
c. Patients who showed at least partial response about 100 days after stem cell transplantation were randomized in a 1:1 ratio after completing consolidation therapy.
d. After about 350 deaths or about 5 years after the second randomization (whichever is first).
e. See Table 1 for the duration of the follow-up observation for the individual outcomes.
ASCT: autologous stem cell transplantation; G-BA: Federal Joint Committee; D-VTd: daratumumab + bortezomib + thalidomide + dexamethasone; n: patients included; VTd: bortezomib + thalidomide + dexamethasone

Figure 1: CASSIOPEIA, schematic diagram of the study design

As described in the dossier assessment of daratumumab, the CASSIOPEIA study comprises 2 parts (see Figure 1).

- Part 1: induction therapy, high-dose therapy with subsequent ASCT, consolidation therapy

Patients in both intervention arm and comparator arm initially received 4 cycles of induction therapy (each lasting 28 days) with D-VTd and VTd, respectively. Provided no disease progression was observed, this was followed by stem cell mobilization. Patients who were ineligible for stem cell mobilization or who exhibited disease progression had to terminate treatment and were continued to be observed. After stem cell collection, patients received high-dose chemotherapy with melphalan. The stem cells were then reinfused. At 30 to 60 days after stem cell transplantation, patients whom the physician deemed able to tolerate systemic follow-up therapy received 2 more cycles of consolidation therapy with the allocated treatment regimen.

- Part 2: maintenance therapy

For maintenance therapy in Part 2 of the CASSIOPEIA study, patients who exhibited at least partial response at the time point 100 days after stem cell transplantation were randomized in a 1:1 ratio after completing consolidation therapy and allocated to either daratumumab monotherapy or observation without further treatment for a period of no more than 2 years (see Figure 1). This part of the study is still ongoing.

Data cut-offs

The company presented 2 data cut-offs for the assessment of the CASSIOPEIA study:

- First data cut-off (19 June 2018): final data cut-off of Part 1 of the CASSIOPEIA study
- Second data cut-off (1 May 2019): data cut-off subsequently requested by the European Medicines Agency (EMA) with analyses on the outcomes “overall survival”, “progression-free survival” and “time to disease progression”

The company presented results on all patient-relevant outcomes for the first data cut-off. The present addendum presents the results on this data cut-off. For the outcome “overall survival”, which was analysed in accordance with the first randomization even after the second randomization in Part 2 of the study, the results of the second data cut-off are additionally presented.

CASSIOPEIA study is unsuitable to answer the research question of the benefit assessment

As already explained in benefit assessment A20-15, the CASSIOPEIA study is unsuitable to answer the research question of the benefit assessment [1]. The Part 1 of the CASSIOPEIA study presented by the company did not completely implement the ACT specified by the G-BA (treatment consisting of induction, ASCT and maintenance [9]), as only the treatment until the

start of the maintenance therapy was investigated. The maintenance therapy (daratumumab monotherapy versus observation without therapy) is subject of Part 2 of the study and does not concur with the ACT specified by the G-BA, which defined lenalidomide as maintenance therapy. First-line therapy in the therapeutic indication consists of the complete line of treatment including maintenance therapy [10-13]; thus, the separate assessment of Part 1 of the CASSIOPEIA study without maintenance therapy does not comprise the complete first-line therapy.

Analyses on overall survival presented by the company are unsuitable to draw conclusions for Part 1 of the study

Regardless of the question of the missing implementation of the ACT in the CASSIOPEIA study, the analyses of both data cut-offs on the outcome overall survival presented by the company are also unsuitable to draw conclusions exclusively for Part 1 of the study (without maintenance therapy). This is explained below.

The outcome "overall survival" was observed beyond the second randomization for all patients until the end of the study. The analysis was conducted in accordance with the original randomization. According to the clinical study report, the first data cut-off was only conducted after all patients had undergone an assessment of response 100 days after ASCT or had already discontinued treatment at this time point. Hence, it can be assumed that already at the first data cut-off, all patients who were eligible for rerandomization in Part 2 of the study had started inadequate maintenance therapy.

The first patient was randomized into the study on 22 September 2015, and the last patient on 1 August 2017. The median treatment duration of the patients in Part 1 of the CASSIOPEIA study was about 9 months, before they were rerandomized shortly afterwards in Part 2 of the study. Based on these data, it can be assumed that the patients were successively randomized to the second part of the CASSIOPEIA study from around mid-2016 onwards, so that the first patients had already been in Part 2 of the study for about 2 years at the time of the first data cut-off (19 June 2018) and for about 3 years at the time of the second data cut-off (1 May 2019). The median observation period for overall survival was almost 19 months at the first data cut-off and about 29 months at the second data cut-off. Therefore, when interpreting the results for the outcome "overall survival", the problem for both data cut-offs is that a large proportion of the patients included had already been treated with inadequate maintenance therapy over a long period of time. Thus, on the basis of the presented analyses conducted by the company on overall survival, it remains unclear how the survival times of the included patients would have developed in the CASSIOPEIA study under an adequate maintenance therapy in accordance with the ACT specified by the G-BA. This should be seen in particular against the background that the survival time curves only separate after about 1 year (see Figure 2 and Figure 3), i.e. only after the patients were rerandomized in Part 2 of the CASSIOPEIA study.

Planned duration of follow-up observation

Table 1 shows the planned duration of follow-up observation of the patients for the individual outcomes.

Table 1: Planned duration of follow-up observation – RCT, direct comparison: daratumumab + bortezomib + thalidomide + dexamethasone vs. bortezomib + thalidomide + dexamethasone

Study **Outcome category** **Outcome**	**Planned follow-up observation**
CASSIOPEIA (Part 1)	
Mortality	
Overall survival	Until end of study[a], death or withdrawal of consent (whichever is first)
Morbidity	
Symptoms/health status (EORTC QLQ-C30 symptom scales/EQ-5D VAS)	Until 100 days after ASCT
Health-related quality of life (EORTC QLQ-C30 functional scales)	Until 100 days after ASCT
Side effects	
All outcomes in the category of side effects	Until 30 days after the last dose of the study medication (Part 1 of the study) or until withdrawal of consent or until start of subsequent myeloma therapy (whichever is first) or until the day of the second randomization
a. The outcome "overall survival" is analysed in accordance with randomization in Part 1 of the study even after rerandomization in Part 2 of the study. ASCT: autologous stem cell transplantation; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life-5 Dimensions; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus	

In the CASSIOPEIA study, overall survival is recorded until the end of the study or until death. The observation period thus not only covers Part 1 of the CASSIOPEIA study, but also extends into Part 2 of the study (see previous section).

The outcomes on morbidity, health-related quality of life and side effects are observed only up to 100 days after ASCT or at most until the second randomization and thus allow the assessment of the results of Part 1 of the CASSIOPEIA study (consisting of induction, ASCT, consolidation, but without subsequent maintenance therapy).

Characteristics of the study population

Table 2 shows the characteristics of the patients in the CASSIOPEIA study.

Table 2: Characteristics of the study population – RCT, direct comparison: daratumumab + bortezomib + thalidomide + dexamethasone vs. bortezomib + thalidomide + dexamethasone

Study Characteristic Category	Daratumumab + bortezomib + thalidomide + dexamethasone N[a] = 543	Bortezomib + thalidomide + dexamethasone N[a] = 542
CASSIOPEIA		
Age [years], mean (SD)	57 (7)	57 (7)
< 50 years, n (%)	83 (15)	90 (17)
≥ 50 to 65 years, n (%)	460 (85)	452 (83)
Sex [F/M], %	42/58	41/59
Family origin, n (%)	ND	ND
Geographical region, n (%)		
Europe	543 (100)	542 (100)
ECOG PS, n (%)		
0	265 (49)	257 (47)
1	225 (41)	230 (42)
2	53 (10)	55 (10)
ISS[b], n (%)		
I	204 (38)	228 (42)
II	255 (47)	233 (43)
III	84 (16)	81 (15)
Cytogenetic risk[c], n (%)		
High risk	82 (15)	86 (16)
Standard risk	460 (85)	454 (84)
Disease duration: time between first diagnosis and randomization [months], mean (SD)	1.3 (3.0)	1.4 (2.2)
Number of lytic bone lesions, n (%)		
None	81 (15)	86 (16)
1 to 3	176 (33)	153 (28)
4 to 6	98 (18)	110 (20)
> 7	185 (34)	191 (35)
Treatment discontinuation[d], n (%)	75 (14)	101 (19)
Study discontinuation[d], n (%)	23 (4)	43 (8)

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. ISS is based on the serum levels of beta 2 microglobulin and albumin [14].
c. Cytogenetic risk is based on FISH or karyotyping, using the following high-risk markers: deletion del(17p) and t(4;14).
d. The information refers to Part 1 of the CASSIOPEIA study (consisting of induction therapy, ASCT and consolidation therapy), which is subject of the present assessment.

ASCT: autologous stem cell transplantation; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; FISH: fluorescence in situ hybridization; ISS: International Staging System; M: male; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The patient characteristics between both treatment arms of the CASSIOPEIA study are comparable. The mean age of the patients was 57 years. The proportion of women in both study arms was about 42%. All patients included were from Europe and the majority (about 90%) had an Eastern Cooperative Oncology Group Performance Status of 0 or 1. About 40% of the patients had tumours with International Staging System (ISS) stage I, about 45% with ISS stage II and about 15% with ISS stage III.

Table 3 shows the mean and median treatment duration of the patients as well as the mean and median observation period for individual outcomes.

Table 3: Information on the course of the study – RCT, direct comparison: daratumumab + bortezomib + thalidomide + dexamethasone vs. bortezomib + thalidomide + dexamethasone

Study **Duration of the study phase** **Outcome category** **Data cut-off**	**Daratumumab + bortezomib + thalidomide + dexamethasone**	**Bortezomib + thalidomide + dexamethasone**
CASSIOPEIA		
Treatment duration (induction, ASCT, consolidation) [months]	N = 536	N = 538
Median [min; max]	8.9 [7.0; 12.0]	8.7 [6.4; 11.5]
Mean (SD)	8.9 (0.7)	8.8 (0.7)
Observation period [months]	N = 543	N = 542
Overall survival		
First data cut-off: 19 June 2018		
Median [min; max]	18.8 [ND]	18.9 [ND]
Mean (SD)	ND	ND
Second data cut-off: 1 May 2019		
Median [min; max]	29.3 [ND]	29.2 [ND]
Mean (SD)	ND	ND
Morbidity, health-related quality of life (EQ-5D/EORTC QLQ-C30)		
First data cut-off		
Median [min; max]	8.8 [ND]	8.6 [ND]
Mean (SD)	ND	ND
Side effects		
First data cut-off		
Median [min; max]	9.9 [ND]	9.7 [ND]
Mean (SD)	ND	ND

ASCT: autologous stem cell transplantation; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life-5 Dimensions; max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

In the CASSIOPEIA study, there are no relevant differences between the treatment arms in the median and mean treatment period (Part 1) and the median observation period at outcome level.

2.2 Results

In accordance with the G-BA's commission, the results of the CASSIOPEIA study are presented. The following patient-relevant outcomes were to be considered in the assessment:

- Mortality
  - overall survival
- Morbidity
  - symptoms measured with the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) symptom scales
  - health status measured with the European Quality of Life-5 Dimensions (EQ-5D) visual analogue scale (VAS)
- Health-related quality of life
  - health-related quality of life measured with the EORTC QLQ-C30 functional scales
- Side effects
  - serious adverse events (SAEs)
  - severe adverse events (AEs) (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to AEs (at least one drug component)

Table 4, Table 5 and Table 6 summarize the results of the comparison of D-VTd versus VTd in the CASSIOPEIA study.

Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. The Kaplan-Meier curves on the event time analyses of the outcomes considered are presented in 0. The results on common AEs of the CASSIOPEIA study can be found in Appendix B.

Table 4: Results (mortality, morbidity, health-related quality of life, time to event) – RCT, direct comparison: daratumumab + bortezomib + thalidomide + dexamethasone vs. bortezomib + thalidomide + dexamethasone (multipage table)

Study **Outcome category** **Outcome**	**Daratumumab + bortezomib + thalidomide + dexamethasone**		**Bortezomib + thalidomide + dexamethasone**		**Daratumumab + bortezomib + thalidomide + dexamethasone vs. bortezomib + thalidomide + dexamethasone**
	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**
CASSIOPEIA					
Mortality (first and second data cut-off)					
Overall survival					
First data cut-off (19 June 2018)	543	NA 14 (2.6)	542	NA 32 (5.9)	0.43 [0.23; 0.80]; 0.007[a]
Second data cut-off (1 May 2019)	543	NA 26 (4.8)	542	NA 48 (8.9)	0.52 [0.33; 0.85]; 0.007[a]
Morbidity (first data cut-off)					
EORTC QLQ-C30 – symptom scales[b]					
Fatigue	543	9.23 [8.81; 9.56] 220 (40.5)	542	8.87 [8.08; 9.59] 228 (42.1)	0.86 [0.71; 1.04]; 0.127[c]
Nausea and vomiting	543	NA 80 (14.7)	542	19.35 [10.71; NC] 81 (14.9)	0.96 [0.70; 1.31]; 0.782[c]
Pain	543	12.03 [12.03; NC] 114 (21.0)	542	NA [9.69; NC] 138 (25.5)	0.74 [0.57; 0.95]; 0.018[c]
Dyspnoea	543	10.35 [9.40; 12.03] 181 (33.3)	542	9.69 [9.07; 10.15] 194 (35.8)	0.85 [0.69; 1.05]; 0.126[c]
Insomnia	543	13.18 [10.35; 13.18] 120 (22.1)	542	10.81 [10.09; NC] 132 (24.4)	0.86 [0.67; 1.11]; 0.250[c]
Appetite loss	543	NA 69 (12.7)	542	NA [19.35; NC] 59 (10.9)	1.16 [0.82; 1.66]; 0.408[c]
Constipation	543	9.53 [9.04; 10.28] 207 (38.1)	542	9.23 [8.64; 9.59] 216 (39.9)	0.88 [0.73; 1.08]; 0.216[c]
Diarrhoea	543	10.71 [10.45; NC] 82 (15.1)	542	NA 66 (12.2)	1.17 [0.84; 1.63]; 0.345[c]
Health-related quality of life (first data cut-off)					
EORTC QLQ-C30 – functional scales[b]					
Global health status	543	13.18 [11.07; 13.18] 120 (22.1)	542	NA [10.05; NC] 139 (25.6)	0.77 [0.60; 0.99]; 0.043[c]
Physical functioning	543	13.18 [10.35; 13.18] 143 (26.3)	542	10.42 [10.05; 25.56] 142 (26.2)	0.96 [0.75; 1.21]; 0.707[c]
Role functioning	543	13.18 [10.15; 13.18] 152 (28.0)	542	10.28 [9.59; NC] 164 (30.3)	0.84 [0.67; 1.05]; 0.116[c]

Table 4: Results (mortality, morbidity, health-related quality of life, time to event) – RCT, direct comparison: daratumumab + bortezomib + thalidomide + dexamethasone vs. bortezomib + thalidomide + dexamethasone (multipage table)

Study **Outcome category** **Outcome**	**Daratumumab + bortezomib + thalidomide + dexamethasone**		**Bortezomib + thalidomide + dexamethasone**		**Daratumumab + bortezomib + thalidomide + dexamethasone vs. bortezomib + thalidomide + dexamethasone**
	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**
Emotional functioning	543	10.94 [10.65; 13.18] 92 (16.9)	542	NA 97 (17.9)	0.87 [0.65; 1.16]; 0.348[c]
Cognitive functioning	543	9.30 [9.04; 9.66] 210 (38.7)	542	9.13 [8.87; 9.66] 220 (40.6)	0.93 [0.76; 1.12]; 0.436[c]
Social functioning	543	10.12 [9.40; 13.18] 183 (33.7)	542	9.43 [9.00; 9.76] 200 (36.9)	0.84 [0.69; 1.03]; 0.100[c]

a. HR [95% CI] from unstratified Cox proportional hazards model; p-value from unstratified log-rank test.
b. Time to deterioration, defined as an increase in score by ≥ 10 points (for the symptom scales) or a decrease in score by ≥ 10 points (for the functional scales) in comparison with baseline. The questionnaire was recorded at only 3 points in time: at study start, after the end of induction therapy (on day 28 in cycle 4) and on day 100 after ASCT.
c. HR [95% CI], p-value from Cox proportional hazards model with stratification factors ISS staging (I vs. II vs. III), site affiliation (IFM vs. HOVON) and cytogenetic risk (standard risk vs. high risk).

ASCT: autologous stem cell transplantation; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HOVON: Hemato-Oncologie voor Volwassenen Nederland; HR: hazard ratio; IFM: Intergroupe Français du Myélome; ISS: International Staging System; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; vs.: versus

Table 5: Results (morbidity, continuous) – RCT, direct comparison: daratumumab + bortezomib + thalidomide + dexamethasone vs. bortezomib + thalidomide + dexamethasone

Study Outcome category Outcome	Daratumumab + bortezomib + thalidomide + dexamethasone			Bortezomib + thalidomide + dexamethasone			Daratumumab + bortezomib + thalidomide + dexamethasone vs. bortezomib + thalidomide + dexamethasone
	N[a]	Values at baseline mean (SD)	Change at end of study[b] Mean[c] [95% CI]	N[a]	Values at baseline mean (SD)	Change at end of study[b] Mean[c] [95% CI]	MD[c] [95% CI]; p-value
CASSIOPEIA							
Morbidity (first data cut-off)							
Health status							
EQ-5D VAS[d]	383	61.50 (23.13)	8.6 [6.5; 10.8]	358	61.04 (23.96)	7.7 [5.5; 9.9]	0.9 [−1.4; 3.2]; 0.441

a. Number of patients with values at the end of the study.
b. Referring to Part 1 of the study (follow-up observation until 100 days after ASCT, see Table 1).
c. MMRM analysis with baseline value, visit, treatment, interaction visit x treatment and stratification factors ISS staging (I vs. II vs. III), site affiliation (IFM vs. HOVON) and cytogenetic risk (standard risk vs. high risk). The questionnaire was recorded at only 3 points in time: at study start, after the end of induction therapy (on day 28 in cycle 4) and on day 100 after ASCT.
d. Higher (increasing) values indicate better health status; positive effects (intervention minus control) indicate an advantage for the intervention.

ASCT: autologous stem cell transplantation; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; HOVON: Hemato-Oncologie voor Volwassenen Nederland; IFM: Intergroupe Français du Myélome; ISS: International Staging System; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale; vs.: versus

Table 6: Results (side effects, dichotomous) – RCT, direct comparison: daratumumab + bortezomib + thalidomide + dexamethasone vs. bortezomib + thalidomide + dexamethasone

Study Outcome category Outcome	Daratumumab + bortezomib + thalidomide + dexamethasone		Bortezomib + thalidomide + dexamethasone		Daratumumab + bortezomib + thalidomide + dexamethasone vs. bortezomib + thalidomide + dexamethasone
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
CASSIOPEIA					
Side effects (first data cut-off)					
AEs (supplementary information)	536	535 (99.8)	538	536 (99.6)	–
SAEs	536	251 (46.8)	538	255 (47.4)	0.99 [0.87; 1.13]; 0.892
Severe AEs (CTCAE grade ≥ 3)	536	432 (80.6)	538	409 (76.0)	1.06 [1.00; 1.13]; 0.069
Discontinuation due to AEs[b]	536	124 (23.1)	538	104 (19.3)	1.20 [0.95; 1.51]; 0.135[c]

a. Cochran-Mantel-Haenszel method with stratification factors ISS staging (I vs. II vs. III), site affiliation (IFM vs. HOVON) and cytogenetic risk (standard risk vs. high risk).
b. Discontinuation of at least one drug component.
c. Institute's calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [15]).

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HOVON: Hemato-Oncologie voor Volwassenen Nederland; IFM: Intergroupe Français du Myélome; ISS: International Staging System; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Mortality

Overall survival (first and second data cut-off)

For the outcome "overall survival", both the first and the second data cut-off showed a statistically significant difference in favour of D-VTd in comparison with VTd.

Morbidity

Health status (EQ-5D VAS, mean change from baseline)

There was no statistically significant difference between the treatment groups for the outcome "health status" recorded with the EQ-5D VAS.

Symptoms (EORTC QLQ-C30, symptom scales, time to deterioration by at least 10 points on the respective scale)

For the symptom scales of the EORTC QLQ-C30, no statistically significant differences between the treatment groups were shown in 7 of the total of 8 scales. A statistically significant difference in favour of D-VTd in comparison with VTd was shown for the scale "pain".

Health-related quality of life

EORTC QLQ-C30 (functional scales, time to deterioration by at least 10 points on the respective scale)

For the functional scales of the EORTC QLQ-C30, no statistically significant differences between the treatment groups were shown in 5 of the total of 6 scales. A statistically significant difference in favour of D-VTd in comparison with VTd was shown for the scale "global health status".

Side effects

No statistically significant differences between the treatment groups were shown for the outcomes "SAEs", "severe AEs" (CTCAE grade ≥ 3) and "discontinuation due to AEs" (at least one drug component).

2.3 Summary

The conclusion on the added benefit of daratumumab in combination with bortezomib, thalidomide and dexamethasone from dossier assessment A20-15 is not changed by the present addendum. The CASSIOPEIA study is unsuitable to draw conclusions on the added benefit of D-VTd versus the ACT in adult patients with newly diagnosed multiple myeloma who are eligible for ASCT.

The following Table 7 shows the result of the benefit assessment of daratumumab in combination with bortezomib, thalidomide and dexamethasone under consideration of dossier assessment A20-15 and the present addendum.

Table 7: Daratumumab in combination with bortezomib, thalidomide and 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 eligible for autologous stem cell transplantation[b]	▪ Induction therapy consisting of bortezomib-dexamethasone-based triple combination therapy upon the physician's discretion[c], followed by ▪ high-dose therapy with melphalan and subsequent autologous stem cell transplantation, followed by ▪ maintenance therapy consisting of: lenalidomide	Added benefit not proven
a. Presentation of the respective ACT specified by the G-BA. b. The CASSIOPEIA study included patients only up to 65 years of age. It remains unclear whether the observed effects can be transferred to patients older than 65 years. c. For the induction therapy, there is a discrepancy between the drugs approved for the therapeutic indication and those recommended in the guidelines. In the context of a clinical study, the following combination therapies principally constitute suitable comparators: bortezomib + thalidomide + dexamethasone as well as bortezomib + cyclophosphamide + dexamethasone. Bortezomib in combination with cyclophosphamide and dexamethasone is not approved for the present therapeutic indication. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The G-BA decides on the added benefit.

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Appendix A – Kaplan-Meier curves on results of the CASSIOPEIA study

Mortality

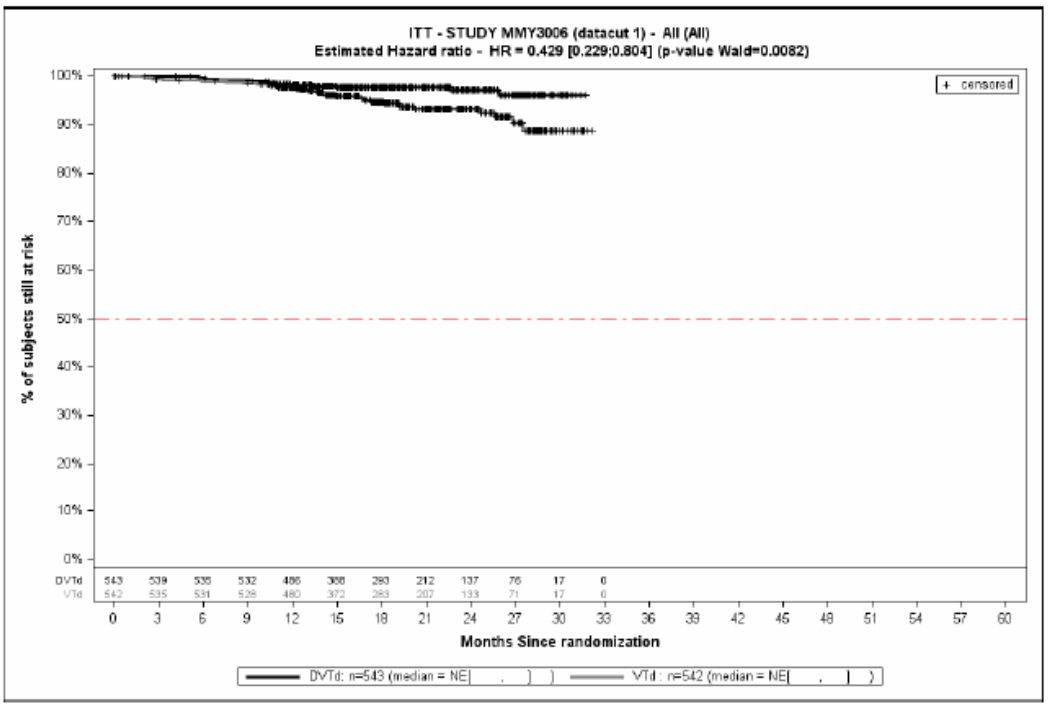

Figure 2: Kaplan-Meier curve on overall survival, data cut-off 1 (19 June 2018)

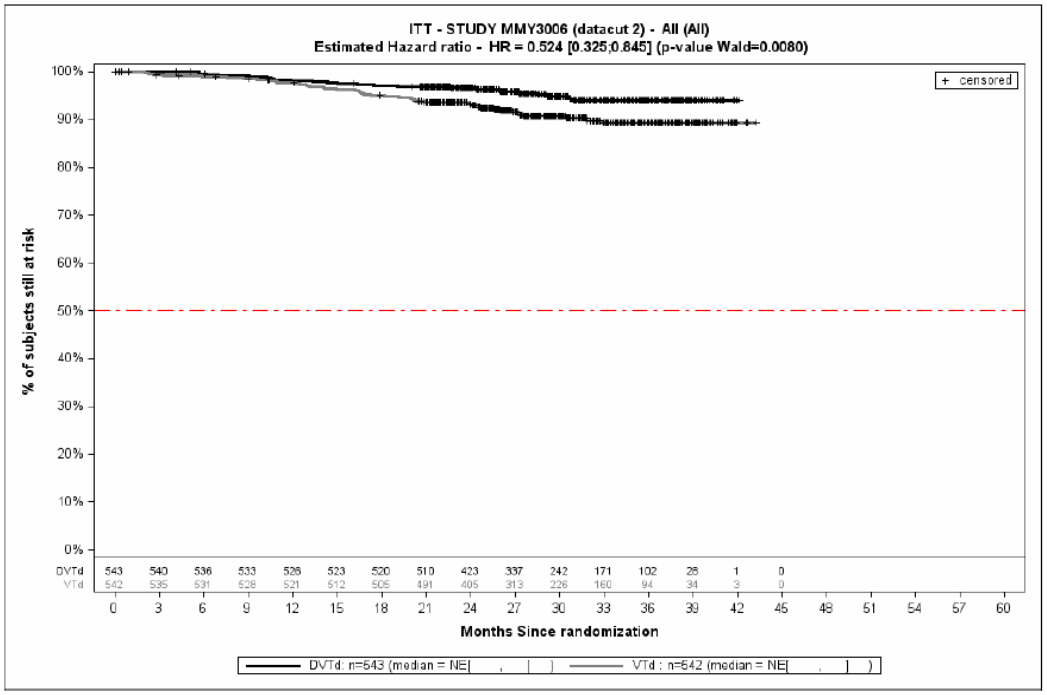

Figure 3: Kaplan-Meier curve on overall survival, data cut-off 2 (1 May 2019)

Morbidity, data cut-off 1; 19 June 2018

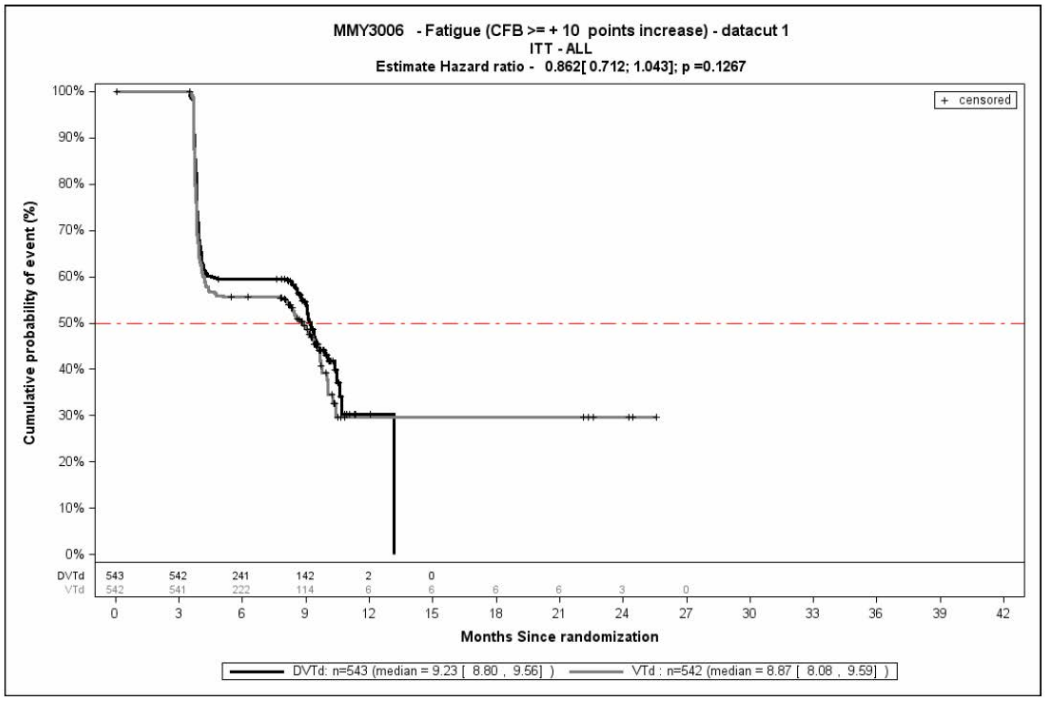

Figure 4: Kaplan-Meier curve on symptoms, outcome "fatigue" (EORTC QLQ-C30, deterioration by ≥ 10 points)

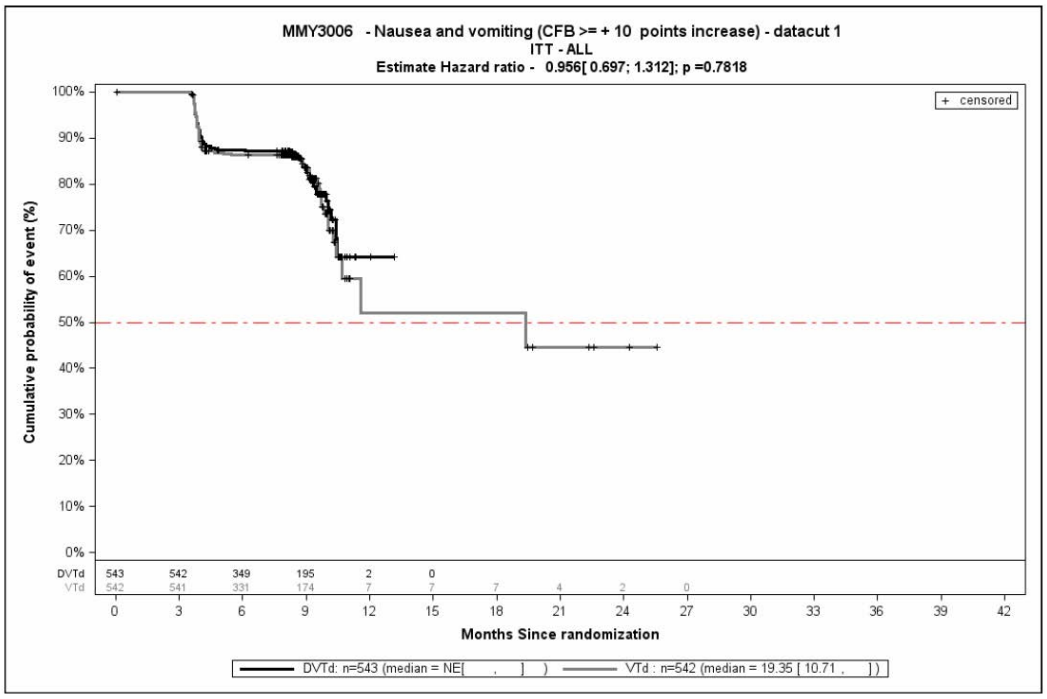

Figure 5: Kaplan-Meier curve on symptoms, outcome "nausea and vomiting" (EORTC QLQ-C30, deterioration by ≥ 10 points)

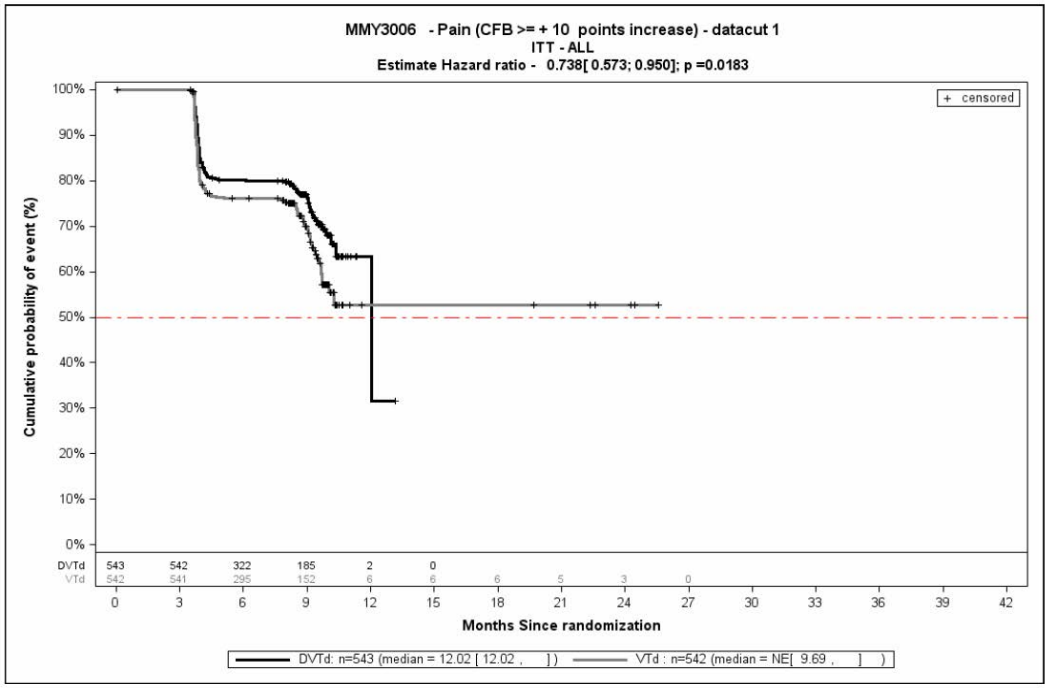

Figure 6: Kaplan-Meier curve on symptoms, outcome "pain" (EORTC QLQ-C30, deterioration by ≥ 10 points)

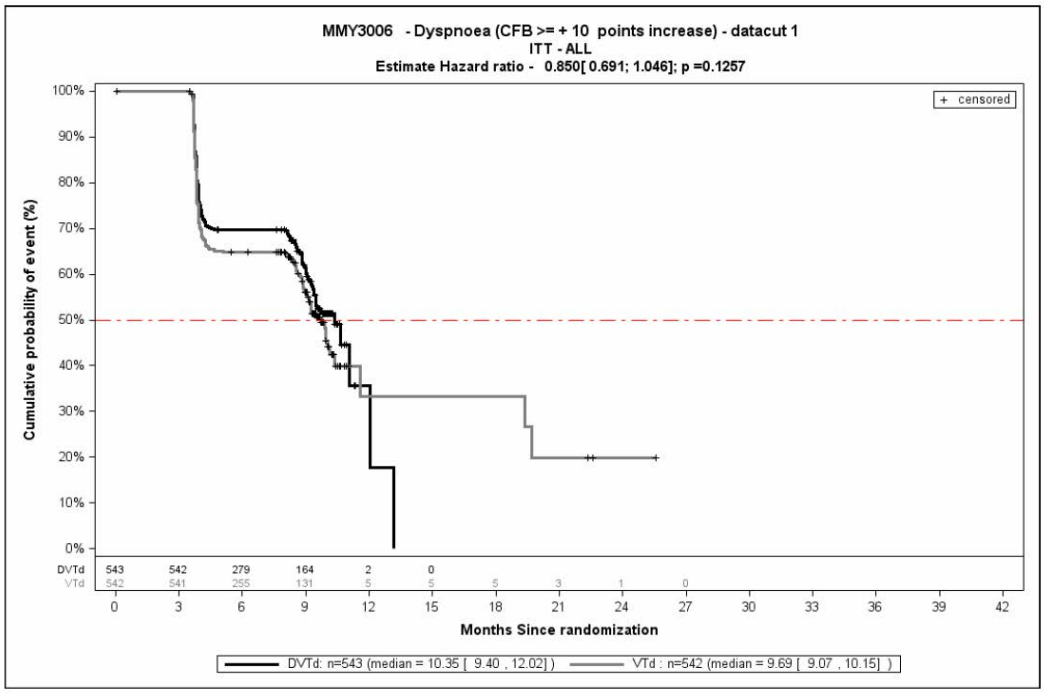

Figure 7: Kaplan-Meier curve on symptoms, outcome "dyspnoea" (EORTC QLQ-C30, deterioration by ≥ 10 points)

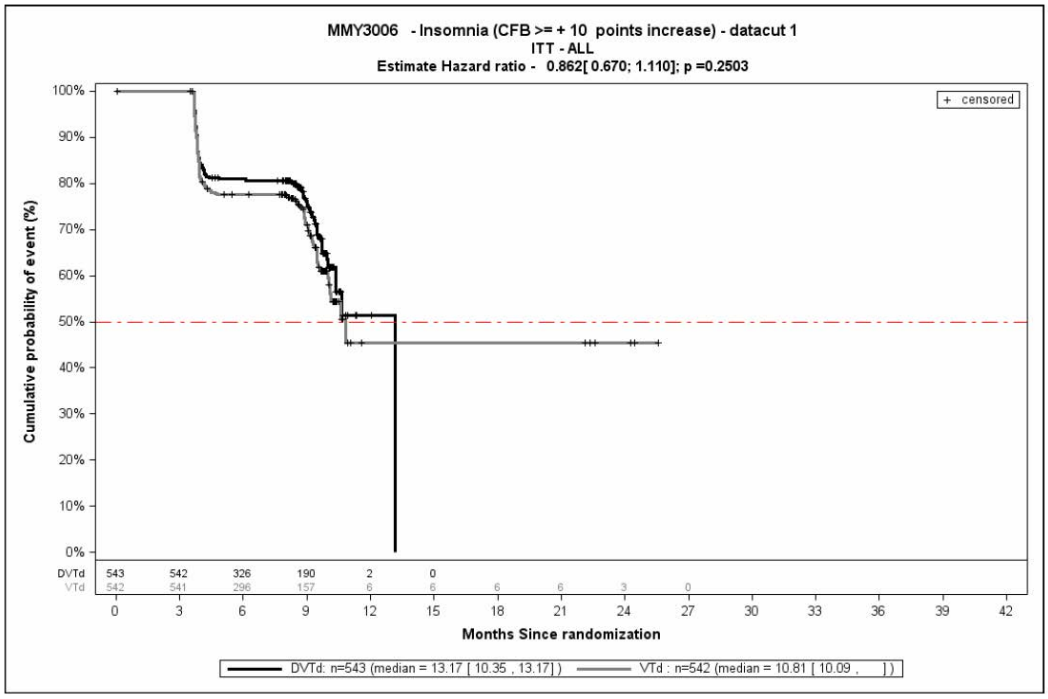

Figure 8: Kaplan-Meier curve on symptoms, outcome "insomnia" (EORTC QLQ-C30, deterioration by ≥ 10 points)

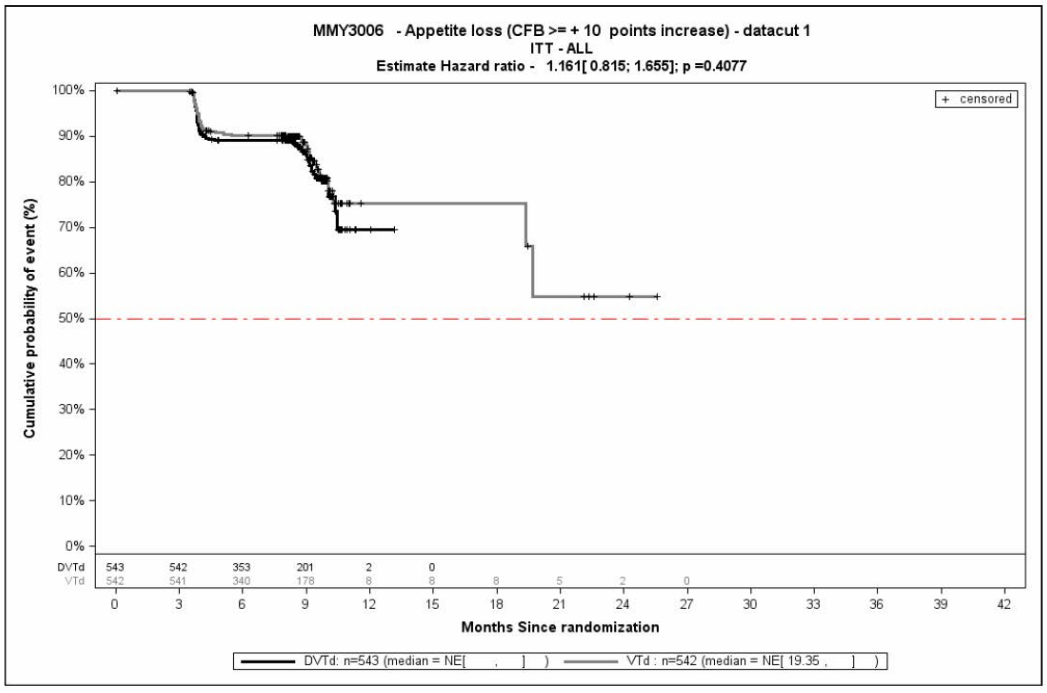

Figure 9: Kaplan-Meier curve on symptoms, outcome "appetite loss" (EORTC QLQ-C30, deterioration by ≥ 10 points)

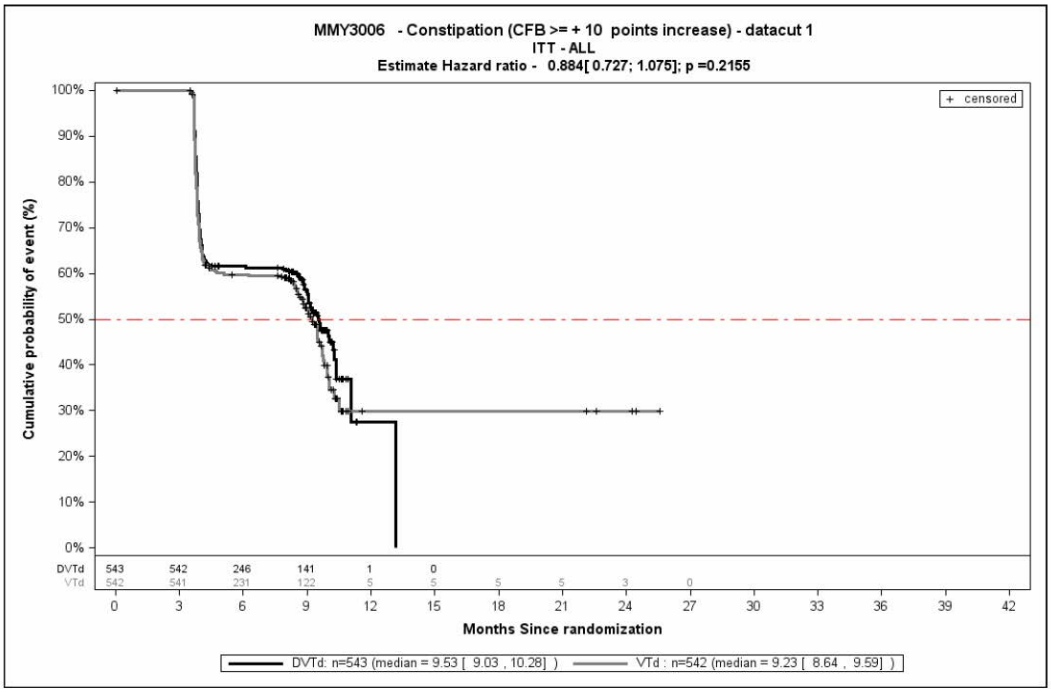

Figure 10: Kaplan-Meier curve on symptoms, outcome "constipation" (EORTC QLQ-C30, deterioration by ≥ 10 points)

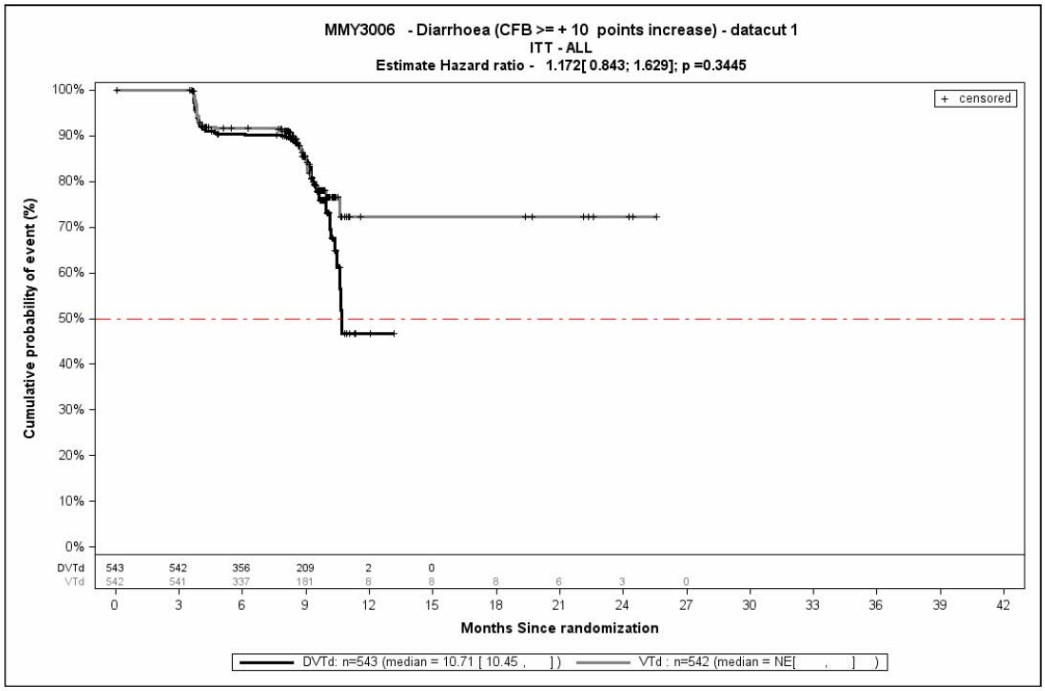

Figure 11: Kaplan-Meier curve on symptoms, outcome "diarrhoea" (EORTC QLQ-C30, deterioration by ≥ 10 points)

Health-related quality of life (data cut-off 1; 19 June 2018)

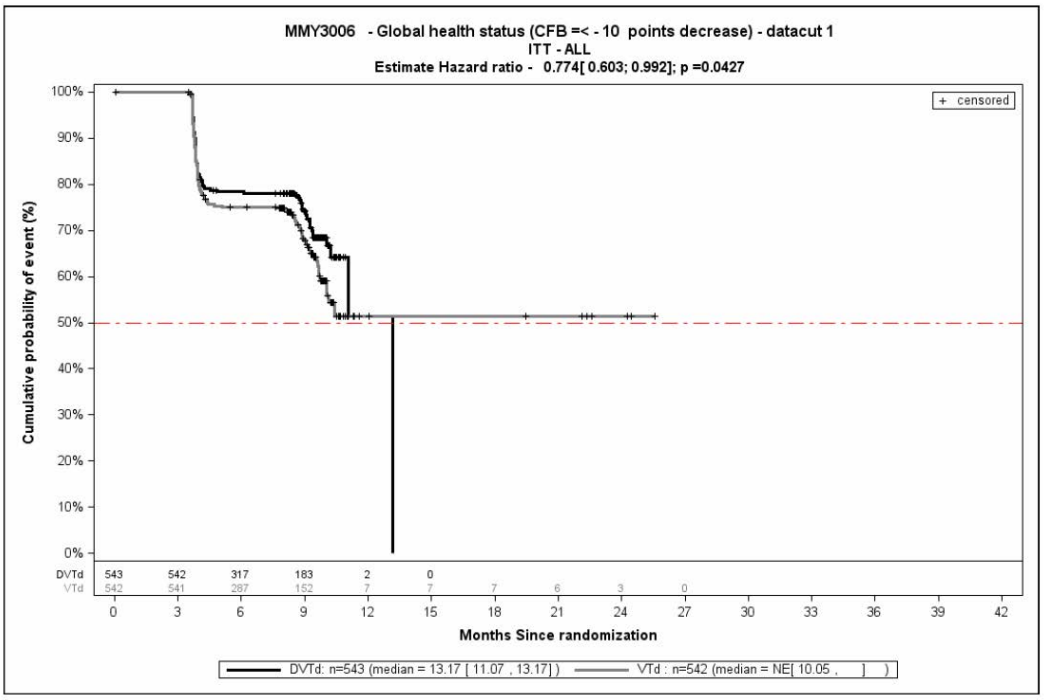

Figure 12: Kaplan-Meier curve on health-related quality of life, outcome "global health status" (EORTC QLQ-C30, deterioration by ≥ 10 points)

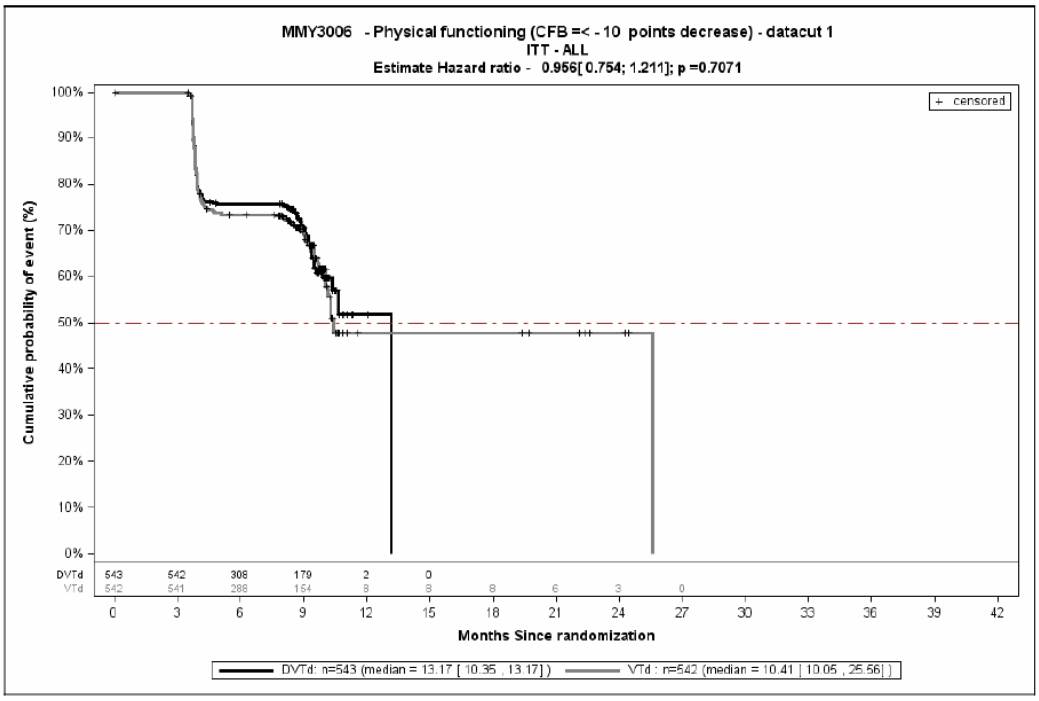

Figure 13: Kaplan-Meier curve on health-related quality of life, outcome "physical functioning" (EORTC QLQ-C30, deterioration by ≥ 10 points)

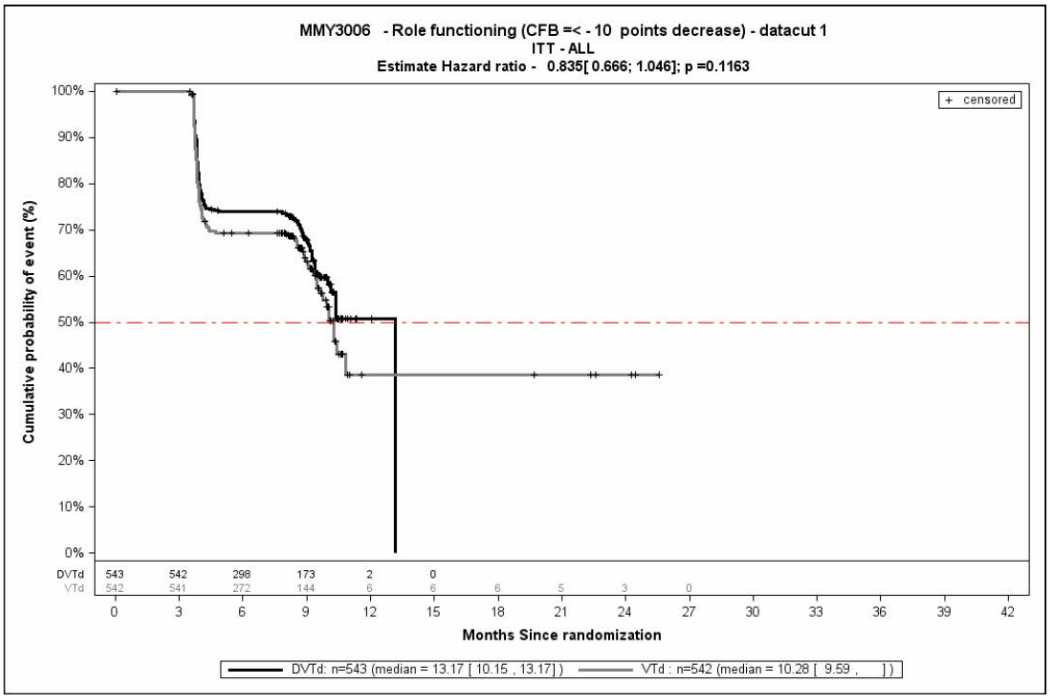

Figure 14: Kaplan-Meier curve on health-related quality of life, outcome "role functioning" (EORTC QLQ-C30, deterioration by ≥ 10 points)

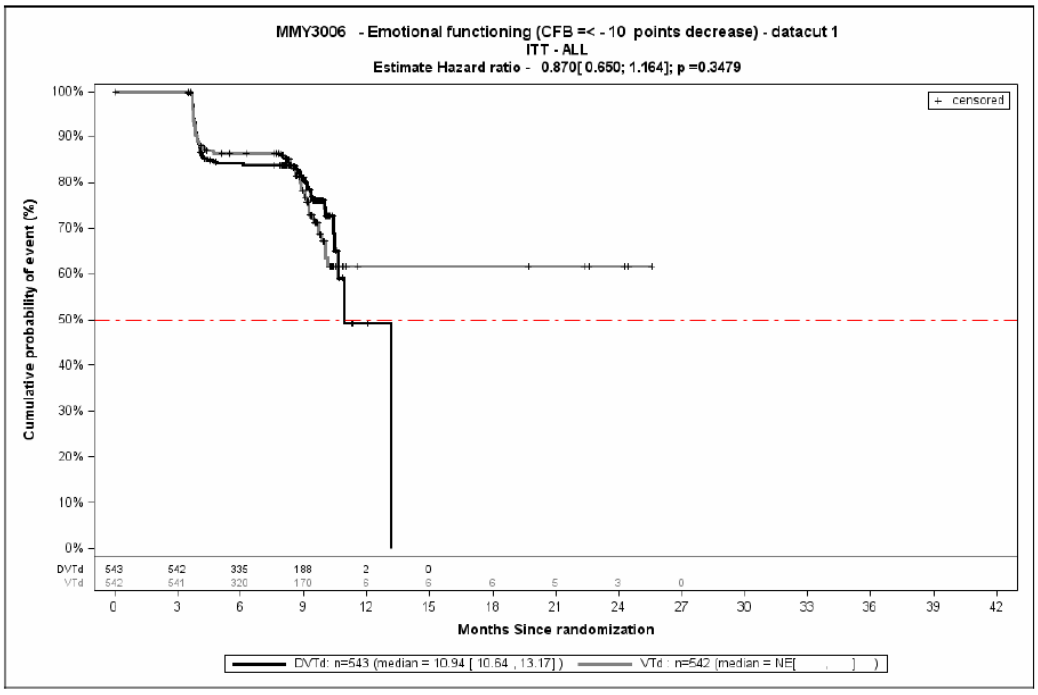

Figure 15: Kaplan-Meier curve on health-related quality of life, outcome "emotional functioning" (EORTC QLQ-C30, deterioration by ≥ 10 points)

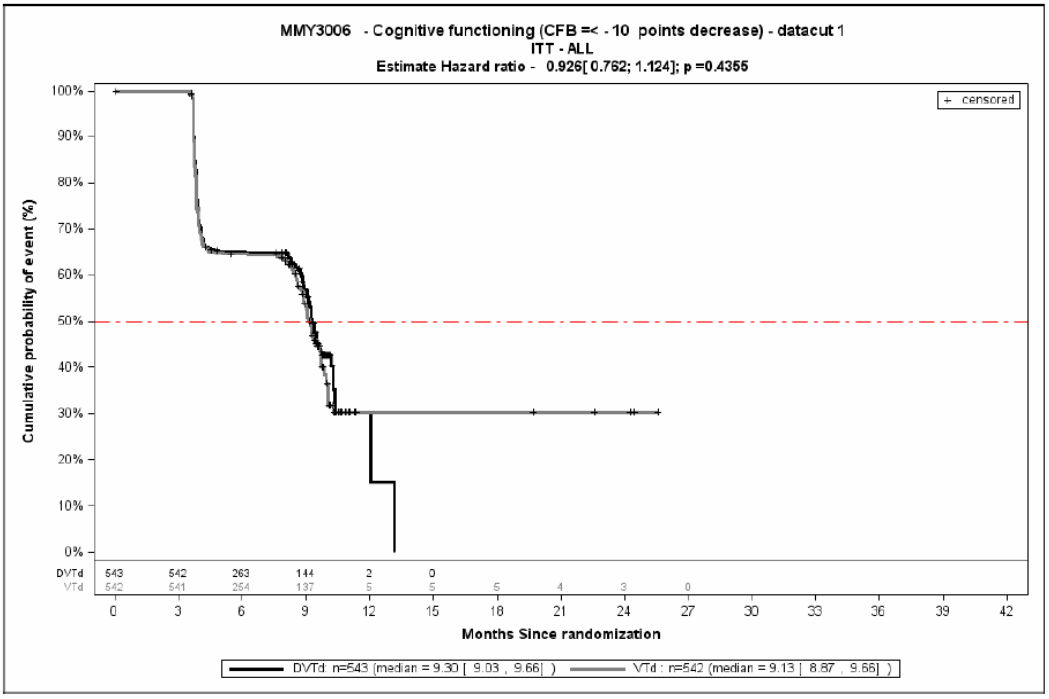

Figure 16: Kaplan-Meier curve on health-related quality of life, outcome "cognitive functioning" (EORTC QLQ-C30, deterioration by ≥ 10 points)

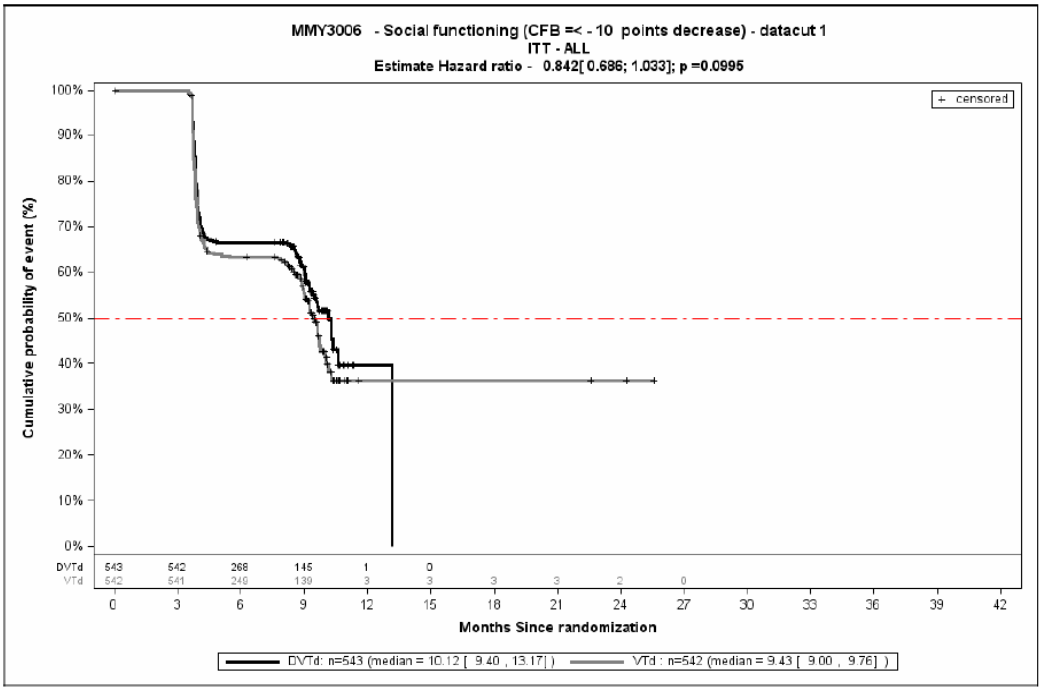

Figure 17: Kaplan-Meier curve on health-related quality of life, outcome "social functioning" (EORTC QLQ-C30, deterioration by ≥ 10 points)

Appendix B – Results on side effects in the CASSIOPEIA study

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

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

For the outcome "discontinuation due to AEs", all events (SOCs/PTs) that resulted in discontinuation (of at least one drug component) are presented.

Table 8: Common AEs[a] – RCT, direct comparison: daratumumab + bortezomib + thalidomide + dexamethasone vs. bortezomib + thalidomide + dexamethasone, data cut-off 1: 19 June 2018 (multipage table)

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**Daratumumab + bortezomib + thalidomide + dexamethasone N = 536**	**Bortezomib + thalidomide + dexamethasone N = 538**
CASSIOPEIA		
Overall AE rate	535 (99.8)	536 (99.6)
Nervous system disorders	437 (81.5)	456 (84.8)
Peripheral sensory neuropathy	314 (58.6)	340 (63.2)
Paraesthesia	118 (22.0)	108 (20.1)
Tremor	71 (13.2)	58 (10.8)
Dysgeusia	49 (9.1)	34 (6.3)
Headache	42 (7.8)	43 (8.0)
Dizziness	34 (6.3)	32 (5.9)
Neuralgia	18 (3.4)	21 (3.9)
Neuropathy peripheral	13 (2.4)	12 (2.2)
Hyperaesthesia	12 (2.2)	3 (0.6)
Hypoaesthesia	12 (2.2)	16 (3.0)
Syncope	11 (2.1)	6 (1.1)
Dysaesthesia	10 (1.9)	11 (2.0)
Somnolence	10 (1.9)	13 (2.4)
Disturbance in attention	8 (1.5)	12 (2.2)
Sciatica	7 (1.3)	14 (2.6)
Gastrointestinal disorders	431 (80.4)	416 (77.3)
Constipation	272 (50.7)	262 (48.7)
Nausea	162 (30.2)	130 (24.2)
Diarrhoea	103 (19.2)	89 (16.5)
Vomiting	87 (16.2)	52 (9.7)
Stomatitis	86 (16.0)	104 (19.3)
Abdominal pain	36 (6.7)	22 (4.1)
Abdominal pain upper	32 (6.0)	29 (5.4)
Dry mouth	27 (5.0)	20 (3.7)
Dyspepsia	18 (3.4)	18 (3.3)
Mouth ulceration	16 (3.0)	17 (3.2)
Haemorrhoids	14 (2.6)	15 (2.8)
Abdominal distension	13 (2.4)	10 (1.9)
Gastrooesophageal reflux disease	7 (1.3)	15 (2.8)
General disorders and administration site conditions	414 (77.2)	398 (74.0)
Asthenia	171 (31.9)	155 (28.8)
Oedema peripheral	162 (30.2)	148 (27.5)

Table 8: Common AEs[a] – RCT, direct comparison: daratumumab + bortezomib + thalidomide + dexamethasone vs. bortezomib + thalidomide + dexamethasone, data cut-off 1: 19 June 2018 (multipage table)

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**Daratumumab + bortezomib + thalidomide + dexamethasone N = 536**	**Bortezomib + thalidomide + dexamethasone N = 538**
Pyrexia	140 (26.1)	114 (21.2)
Fatigue	70 (13.1)	86 (16.0)
Chills	47 (8.8)	22 (4.1)
Malaise	36 (6.7)	24 (4.5)
Influenza like illness	33 (6.2)	29 (5.4)
Injection site erythema	32 (6.0)	28 (5.2)
Chest pain	16 (3.0)	22 (4.1)
Chest discomfort	12 (2.2)	1 (0.2)
General physical health deterioration	10 (1.9)	5 (0.9)
Face oedema	8 (1.5)	11 (2.0)
Injection site rash	7 (1.3)	11 (2.0)
Infections and infestations	351 (65.5)	306 (56.9)
Bronchitis	102 (19.0)	66 (12.3)
Nasopharyngitis	34 (6.3)	19 (3.5)
Pneumonia	33 (6.2)	23 (4.3)
Upper respiratory tract infection	33 (6.2)	18 (3.3)
Rhinitis	32 (6.0)	16 (3.0)
Viral upper respiratory tract infection	26 (4.9)	14 (2.6)
Herpes zoster	20 (3.7)	17 (3.2)
Sinusitis	19 (3.5)	16 (3.0)
Conjunctivitis	18 (3.4)	14 (2.6)
Urinary tract infection	17 (3.2)	20 (3.7)
Lung infection	16 (3.0)	7 (1.3)
Gastroenteritis	15 (2.8)	5 (0.9)
Sepsis	15 (2.8)	15 (2.8)
Hordeolum	14 (2.6)	19 (3.5)
Influenza	13 (2.4)	8 (1.5)
Pharyngitis	12 (2.2)	6 (1.1)
Folliculitis	10 (1.9)	6 (1.1)
Blood and lymphatic system disorders	303 (56.5)	253 (47.0)
Neutropenia	157 (29.3)	89 (16.5)
Thrombocytopenia	109 (20.3)	73 (13.6)
Lymphopenia	99 (18.5)	67 (12.5)
Anaemia	73 (13.6)	81 (15.1)
Febrile neutropenia	37 (6.9)	28 (5.2)
Leukopenia	27 (5.0)	15 (2.8)

Table 8: Common AEs[a] – RCT, direct comparison: daratumumab + bortezomib + thalidomide + dexamethasone vs. bortezomib + thalidomide + dexamethasone, data cut-off 1: 19 June 2018 (multipage table)

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**Daratumumab + bortezomib + thalidomide + dexamethasone N = 536**	**Bortezomib + thalidomide + dexamethasone N = 538**
Febrile bone marrow aplasia	9 (1.7)	17 (3.2)
Respiratory, thoracic and mediastinal disorders	259 (48.3)	185 (34.4)
Cough	90 (16.8)	49 (9.1)
Dyspnoea	77 (14.4)	66 (12.3)
Rhinorrhoea	45 (8.4)	25 (4.6)
Dyspnoea exertional	28 (5.2)	26 (4.8)
Lung disorder	16 (3.0)	9 (1.7)
Pulmonary embolism	15 (2.8)	23 (4.3)
Oropharyngeal pain	14 (2.6)	13 (2.4)
Hiccups	11 (2.1)	14 (2.6)
Rhinitis allergic	10 (1.9)	0 (0)
Skin and subcutaneous tissue disorders	255 (47.6)	222 (41.3)
Rash	86 (16.0)	67 (12.5)
Erythema	61 (11.4)	47 (8.7)
Dry skin	27 (5.0)	31 (5.8)
Pruritus	25 (4.7)	17 (3.2)
Urticaria	22 (4.1)	15 (2.8)
Eczema	18 (3.4)	7 (1.3)
Hyperhidrosis	13 (2.4)	12 (2.2)
Rash maculo-papular	13 (2.4)	12 (2.2)
Rash generalised	12 (2.2)	18 (3.3)
Toxic skin eruption	4 (0.7)	11 (2.0)
Musculoskeletal and connective tissue disorders	245 (45.7)	252 (46.8)
Bone pain	70 (13.1)	82 (15.2)
Back pain	59 (11.0)	55 (10.2)
Pain in extremity	37 (6.9)	42 (7.8)
Myalgia	33 (6.2)	30 (5.6)
Muscle spasms	29 (5.4)	35 (6.5)
Arthralgia	25 (4.7)	27 (5.0)
Musculoskeletal chest pain	17 (3.2)	18 (3.3)
Musculoskeletal pain	17 (3.2)	9 (1.7)
Neck pain	11 (2.1)	9 (1.7)
Muscular weakness	10 (1.9)	14 (2.6)

Table 8: Common AEs[a] – RCT, direct comparison: daratumumab + bortezomib + thalidomide + dexamethasone vs. bortezomib + thalidomide + dexamethasone, data cut-off 1: 19 June 2018 (multipage table)

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**Daratumumab + bortezomib + thalidomide + dexamethasone N = 536**	**Bortezomib + thalidomide + dexamethasone N = 538**
Vascular disorders	157 (29.3)	131 (24.3)
Hypertension	51 (9.5)	29 (5.4)
Deep vein thrombosis	28 (5.2)	31 (5.8)
Hypotension	24 (4.5)	17 (3.2)
Hot flush	14 (2.6)	9 (1.7)
Orthostatic hypotension	14 (2.6)	10 (1.9)
Phlebitis	10 (1.9)	7 (1.3)
Psychiatric disorders	141 (26.3)	153 (28.4)
Insomnia	61 (11.4)	78 (14.5)
Anxiety	58 (10.8)	46 (8.6)
Depression	22 (4.1)	15 (2.8)
Agitation	11 (2.1)	11 (2.0)
Irritability	7 (1.3)	11 (2.0)
Metabolism and nutrition disorders	125 (23.3)	121 (22.5)
Decreased appetite	39 (7.3)	36 (6.7)
Hypokalaemia	30 (5.6)	19 (3.5)
Diabetes mellitus	11 (2.1)	10 (1.9)
Hyperkalaemia	10 (1.9)	11 (2.0)
Hyperglycaemia	7 (1.3)	12 (2.2)
Hyponatraemia	6 (1.1)	12 (2.2)
Eye disorders	99 (18.5)	83 (15.4)
Vision blurred	25 (4.7)	31 (5.8)
Dry eye	13 (2.4)	11 (2.0)
Chalazion	12 (2.2)	16 (3.0)
Investigations	80 (14.9)	78 (14.5)
Weight decreased	33 (6.2)	34 (6.3)
Weight increased	16 (3.0)	20 (3.7)
Alanine aminotransferase increased	10 (1.9)	15 (2.8)
Aspartate aminotransferase increased	5 (0.9)	11 (2.0)
Ear and labyrinth disorders	66 (12.3)	64 (11.9)
Vertigo	40 (7.5)	44 (8.2)
Tinnitus	15 (2.8)	21 (3.9)
Cardiac disorders	58 (10.8)	54 (10.0)
Tachycardia	11 (2.1)	6 (1.1)
Palpitations	10 (1.9)	10 (1.9)
Atrial fibrillation	5 (0.9)	11 (2.0)

Table 8: Common AEs[a] – RCT, direct comparison: daratumumab + bortezomib + thalidomide + dexamethasone vs. bortezomib + thalidomide + dexamethasone, data cut-off 1: 19 June 2018 (multipage table)

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**Daratumumab + bortezomib + thalidomide + dexamethasone N = 536**	**Bortezomib + thalidomide + dexamethasone N = 538**
Immune system disorders	51 (9.5)	33 (6.1)
Hypogammaglobulinaemia	36 (6.7)	19 (3.5)
Hypersensitivity	10 (1.9)	6 (1.1)
Injury, poisoning and procedural complications	46 (8.6)	49 (9.1)
Renal and urinary disorders	42 (7.8)	40 (7.4)
Dysuria	11 (2.1)	6 (1.1)
Hepatobiliary disorders	23 (4.3)	23 (4.3)
Hepatocellular injury	12 (2.2)	14 (2.6)
Reproductive system and breast disorders	17 (3.2)	23 (4.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9 (1.7)	10 (1.9)
Endocrine disorders	4 (0.7)	16 (3.0)
Surgical and medical procedures	4 (0.7)	11 (2.0)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 20.0; SOC and PT notation taken from MedDRA without adaptation.

AE: adverse event; 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; vs.: versus

Table 9: Common SAEs[a] – RCT, direct comparison: daratumumab + bortezomib + thalidomide + dexamethasone vs. bortezomib + thalidomide + dexamethasone, data cut-off 1: 19 June 2018

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**Daratumumab + bortezomib + thalidomide + dexamethasone N = 536**	**Bortezomib + thalidomide + dexamethasone N = 538**
CASSIOPEIA		
Overall rate of SAEs	251 (46.8)	255 (47.4)
Infections and infestations	80 (14.9)	67 (12.5)
Pneumonia	19 (3.5)	9 (1.7)
Sepsis	7 (1.3)	11 (2.0)
Blood and lymphatic system disorders	57 (10.6)	44 (8.2)
Neutropenia	21 (3.9)	8 (1.5)
Febrile neutropenia	12 (2.2)	15 (2.8)
Thrombocytopenia	12 (2.2)	4 (0.7)
Febrile bone marrow aplasia	7 (1.3)	11 (2.0)
Respiratory, thoracic and mediastinal disorders	38 (7.1)	38 (7.1)
Lung disorder	11 (2.1)	6 (1.1)
Pulmonary embolism	8 (1.5)	20 (3.7)
General disorders and administration site conditions	33 (6.2)	37 (6.9)
Pyrexia	15 (2.8)	23 (4.3)
Nervous system disorders	33 (6.2)	44 (8.2)
Peripheral sensory neuropathy	11 (2.1)	15 (2.8)
Gastrointestinal disorders	27 (5.0)	28 (5.2)
Musculoskeletal and connective tissue disorders	17 (3.2)	18 (3.3)
Cardiac disorders	14 (2.6)	19 (3.5)
Metabolism and nutrition disorders	14 (2.6)	12 (2.2)
Injury, poisoning and procedural complications	12 (2.2)	14 (2.6)
Vascular disorders	11 (2.1)	13 (2.4)
Renal and urinary disorders	8 (1.5)	10 (1.9)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 20.0; SOC and PT notation taken from MedDRA without adaptation.

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; vs.: versus

Table 10: Common severe AEs[a] (CTCAE grade ≥ 3) – RCT, direct comparison: daratumumab + bortezomib + thalidomide + dexamethasone vs. bortezomib + thalidomide + dexamethasone, data cut-off 1: 19 June 2018 (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Daratumumab + bortezomib + thalidomide + dexamethasone N = 536**	**Bortezomib + thalidomide + dexamethasone N = 538**
CASSIOPEIA		
Overall rate of severe AEs (CTCAE grade ≥ 3)	432 (80.6)	409 (76.0)
Blood and lymphatic system disorders	249 (46.5)	196 (36.4)
Neutropenia	148 (27.6)	79 (14.7)
Lymphopenia	91 (17.0)	52 (9.7)
Thrombocytopenia	59 (11 0)	40 (7.4)
Febrile neutropenia	36 (6.7)	28 (5.2)
Leukopenia	18 (3.4)	13 (2.4)
Anaemia	17 (3.2)	22 (4.1)
Febrile bone marrow aplasia	7 (1.3)	12 (2.2)
Gastrointestinal disorders	124 (23.1)	131 (24.3)
Stomatitis	68 (12.7)	88 (16.4)
Nausea	21 (3.9)	12 (2.2)
Diarrhoea	20 (3.7)	10 (1.9)
Vomiting	12 (2.2)	9 (1.7)
Infections and infestations	118 (22.0)	105 (19.5)
Pneumonia	16 (3.0)	12 (2.2)
Sepsis	11 (2.1)	14 (2.6)
Nervous system disorders	73 (13.6)	73 (13.6)
Peripheral sensory neuropathy	47 (8.8)	46 (8.6)
Respiratory, thoracic and mediastinal disorders	43 (8.0)	36 (6.7)
Pulmonary embolism	10 (1.9)	22 (4.1)
Metabolism and nutrition disorders	40 (7.5)	35 (6.5)
Vascular disorders	35 (6.5)	27 (5.0)
Hypertension	22 (4.1)	12 (2.2)
Deep vein thrombosis	5 (0.9)	10 (1.9)
General disorders and administration site conditions	32 (6.0)	38 (7.1)
Pyrexia	14 (2.6)	12 (2.2)
Musculoskeletal and connective tissue disorders	31 (5.8)	29 (5.4)
Back pain	14 (2.6)	9 (1.7)
Bone pain	11 (2.1)	9 (1.7)
Skin and subcutaneous tissue disorders	17 (3.2)	16 (3.0)
Injury, poisoning and procedural complications	14 (2.6)	12 (2.2)

Table 10: Common severe AEs[a] (CTCAE grade ≥ 3) – RCT, direct comparison: daratumumab + bortezomib + thalidomide + dexamethasone vs. bortezomib + thalidomide + dexamethasone, data cut-off 1: 19 June 2018 (multipage table)

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**Daratumumab + bortezomib + thalidomide + dexamethasone N = 536**	**Bortezomib + thalidomide + dexamethasone N = 538**
Psychiatric disorders	14 (2.6)	14 (2.6)
Cardiac disorders	13 (2.4)	19 (3.5)
Investigations	11 (2.1)	12 (2.2)
Renal and urinary disorders	11 (2.1)	9 (1.7)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 20.0; SOC and PT notation taken from MedDRA without adaptation.

AE: adverse event; 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; vs.: versus

Table 11: Discontinuations due to AEs[a] – RCT, direct comparison: daratumumab + bortezomib + thalidomide + dexamethasone vs. bortezomib + thalidomide + dexamethasone, data cut-off 1: 19 June 2018 (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Daratumumab + bortezomib + thalidomide + dexamethasone N = 536**	**Bortezomib + thalidomide + dexamethasone N = 538**
CASSIOPEIA		
Overall rate of discontinuations due to AEs (discontinuation of at least one drug component)	124 (23.1)	104 (19.3)
Nervous system disorders	83 (15.5)	75 (13.9)
Peripheral sensory neuropathy	64 (11.9)	58 (10.8)
Paraesthesia	4 (0.7)	4 (0.7)
Neuralgia	3 (0.6)	4 (0.7)
Autonomic neuropathy	2 (0.4)	0 (0)
Neuropathy peripheral	2 (0.4)	2 (0.4)
Peripheral motor neuropathy	2 (0.4)	1 (0.2)
Transient ischaemic attack	2 (0.4)	0 (0)
Tremor	2 (0.4)	2 (0.4)
Dizziness	1 (0.2)	0 (0)
Encephalopathy	1 (0.2)	0 (0)
Paraparesis	1 (0.2)	0 (0)
Peripheral sensorimotor neuropathy	1 (0.2)	3 (0.6)
Polyneuropathy	1 (0.2)	3 (0.6)
Status epilepticus	1 (0.2)	0 (0)
Syncope	1 (0.2)	0 (0)
Axonal neuropathy	0 (0)	1 (0.2)
Epidural lipomatosis	0 (0)	1 (0.2)
Hypoaesthesia	0 (0)	1 (0.2)
Posterior reversible encephalopathy syndrome	0 (0)	1 (0.2)
Infections and infestations	11 (2.1)	6 (1.1)
Herpes zoster	2 (0.4)	0 (0)
Bronchitis	1 (0.2)	1 (0.2)
Cytomegalovirus infection	1 (0.2)	0 (0)
Cytomegalovirus oesophagitis	1 (0.2)	0 (0)
Device related sepsis	1 (0.2)	0 (0)
Diverticulitis	1 (0.2)	0 (0)
Intestinal sepsis	1 (0.2)	0 (0)
Pneumonia	1 (0.2)	1 (0.2)
Pneumonia haemophilus	1 (0.2)	0 (0)
Scedosporium infection	1 (0.2)	0 (0)
Peritonitis	0 (0)	2 (0.4)

Table 11: Discontinuations due to AEs[a] – RCT, direct comparison: daratumumab + bortezomib + thalidomide + dexamethasone vs. bortezomib + thalidomide + dexamethasone, data cut-off 1: 19 June 2018 (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Daratumumab + bortezomib + thalidomide + dexamethasone N = 536**	**Bortezomib + thalidomide + dexamethasone N = 538**
Sepsis	0 (0)	1 (0.2)
Septic shock	0 (0)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	8 (1.5)	6 (1.1)
Chronic obstructive pulmonary disease	2 (0.4)	0 (0)
Dyspnoea	2 (0.4)	1 (0.2)
Acute respiratory distress syndrome	1 (0.2)	0 (0)
Bronchospasm	1 (0.2)	0 (0)
Interstitial lung disease	1 (0.2)	1 (0.2)
Pulmonary embolism	1 (0.2)	2 (0.4)
Lung disorder	0 (0)	1 (0.2)
Pneumonitis	0 (0)	1 (0.2)
General disorders and administration site conditions	6 (1.1)	3 (0.6)
General physical health deterioration	2 (0.4)	1 (0.2)
Malaise	2 (0.4)	0 (0)
Asthenia	1 (0.2)	0 (0)
Oedema peripheral	1 (0.2)	1 (0.2)
Fatigue	0 (0)	2 (0.4)
Cardiac disorders	5 (0.9)	3 (0.6)
Cardiac failure	2 (0.4)	1 (0.2)
Cardiac arrest	1 (0.2)	0 (0)
Mitral valve prolapse	1 (0.2)	0 (0)
Tachycardia	1 (0.2)	0 (0)
Cardiac amyloidosis	0 (0)	1 (0.2)
Pericardial effusion	0 (0)	1 (0.2)
Skin and subcutaneous tissue disorders	5 (0.9)	3 (0.6)
Drug reaction with eosinophilia and systemic symptoms	1 (0.2)	0 (0)
Erythema	1 (0.2)	0 (0)
Generalised erythema	1 (0.2)	0 (0)
Rash generalised	1 (0.2)	2 (0.4)
Rash morbilliform	1 (0.2)	0 (0)
Cutaneous vasculitis	0 (0)	1 (0.2)
Rash	0 (0)	1 (0.2)

Table 11: Discontinuations due to AEs[a] – RCT, direct comparison: daratumumab + bortezomib + thalidomide + dexamethasone vs. bortezomib + thalidomide + dexamethasone, data cut-off 1: 19 June 2018 (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Daratumumab + bortezomib + thalidomide + dexamethasone N = 536**	**Bortezomib + thalidomide + dexamethasone N = 538**
Blood and lymphatic system disorders	3 (0.6)	1 (0.2)
Thrombocytopenia	2 (0.4)	0 (0)
Neutropenia	1 (0.2)	0 (0)
Haemolytic uraemic syndrome	0 (0)	1 (0.2)
Injury, poisoning and procedural complications	3 (0.6)	0 (0)
Blood stem cell harvest failure	3 (0.6)	0 (0)
Gastrointestinal disorders	2 (0.4)	1 (0.2)
Constipation	1 (0.2)	0 (0)
Pancreatitis	1 (0.2)	0 (0)
Colitis ischaemic	0 (0)	1 (0.2)
Large intestine perforation	0 (0)	1 (0.2)
Metabolism and nutrition disorders	2 (0.4)	1 (0.2)
Hypercalcaemia	1 (0.2)	0 (0)
Hyponatraemia	1 (0.2)	0 (0)
Diabetes mellitus	0 (0)	1 (0.2)
Psychiatric disorders	1 (0.2)	5 (0.9)
Confusional state	1 (0.2)	1 (0.2)
Anxiety	0 (0)	1 (0.2)
Depression	0 (0)	2 (0.4)
Irritability	0 (0)	1 (0.2)
Vascular disorders	1 (0.2)	2 (0.4)
Hypotension	1 (0.2)	0 (0)
Phlebitis	0 (0)	1 (0.2)
Venous thrombosis	0 (0)	1 (0.2)
Ear and labyrinth disorders	0 (0)	1 (0.2)
Deafness	0 (0)	1 (0.2)
Immune system disorders	0 (0)	1 (0.2)
Hypersensitivity	0 (0)	1 (0.2)
Musculoskeletal and connective tissue disorders	0 (0)	4 (0.7)
Arthralgia	0 (0)	1 (0.2)
Muscular weakness	0 (0)	2 (0.4)
Osteonecrosis	0 (0)	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0)	1 (0.2)
Adenocarcinoma in the lungs	0 (0)	1 (0.2)

Table 11: Discontinuations due to AEs[a] – RCT, direct comparison: daratumumab + bortezomib + thalidomide + dexamethasone vs. bortezomib + thalidomide + dexamethasone, data cut-off 1: 19 June 2018 (multipage table)

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**Daratumumab + bortezomib + thalidomide + dexamethasone N = 536**	**Bortezomib + thalidomide + dexamethasone N = 538**
Renal and urinary disorders	0 (0)	2 (0.4)
Acute kidney injury	0 (0)	1 (0.2)
Renal impairment	0 (0)	1 (0.2)

a. Discontinuation of at least one drug component.
b. MedDRA version 20.0; SOC and PT notation taken from MedDRA without adaptation.

AE: adverse event; 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; vs.: versus

Appendix C – Supplementary presentation of responder analyses for the outcome "health status" (EQ-5D)

Table 12: Results (morbidity - results on the outcome "EQ-5D VAS", supplementary presentation) – RCT, direct comparison: daratumumab + bortezomib + thalidomide + dexamethasone vs. bortezomib + thalidomide + dexamethasone

Study **Outcome category** **Outcome**	**Daratumumab + bortezomib + thalidomide + dexamethasone**		**Bortezomib + thalidomide + dexamethasone**		**Daratumumab + bortezomib + thalidomide + dexamethasone vs. bortezomib + thalidomide + dexamethasone**
	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]**
CASSIOPEIA					
Morbidity (first data cut-off)					
Health status (EQ-5D VAS) – supplementary presentation					
Time to deterioration[b]					
7 points	*543*	*10.35 [9.96; NC]* *153 (28.2)*	*542*	*10.42 [9.66; NC]* *152 (28.0)*	*0.92 [0.73; 1.16]; 0.482*
10 points	*543*	*10.35 [10.35; NC]* *150 (27.6)*	*542*	*10.71 [9.66; NC]* *148 (27.3)*	*0.93 [0.74; 1.17]; 0.545*

a. HR [95% CI], p-value from Cox proportional hazards model with stratification factors ISS staging (I vs. II vs. III), site affiliation (IFM vs. HOVON) and cytogenetics (standard risk vs. high risk).
d. Time to deterioration (decrease) of the score by at least 7 or 10 points versus the baseline value. The questionnaire was recorded at only 3 points in time: at study start, after the end of induction therapy (on day 28 in cycle 4) and on day 100 after ASCT.

ASCT: autologous stem cell transplantation; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; HOVON: Hemato-Oncologie voor Volwassenen Nederland; IFM: Intergroupe Français du Myélome; ISS: International Staging System; n: number of patients with event; N: number of analysed patients; NC: not calculable; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus