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Daratumumab (multiple myeloma) –

Addendum to Commission A17-40[1]

Addendum

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

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

IQWiG employees involved in the addendum:

- Ulrike Seay
- Petra Kohlepp
- Christoph Schürmann
- Volker Vervölgyi

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ASCT	autologous stem cell transplantation
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	European Quality of Life-5 Dimensions
FDA	Food and Drug Administration
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
PFS	progression-free survival
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire-Core 30
RCT	randomized controlled trial
SAE	serious adverse event
SCT	stem cell transplantation
SOC	System Organ Class
SPC	Summary of Product Characteristics
VAS	visual analogue scale

1 Background

On 8 January 2018, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A17-40 (Daratumumab – Benefit assessment according to §35a Social Code Book V) [1].

In Module 4 A [2] of its dossier on daratumumab, the pharmaceutical company (hereinafter referred to as "the company") presented the studies POLLUX and CASTOR for the therapeutic indication of multiple myeloma in patients who have received at least one prior therapy.

In the dossier assessment, the POLLUX study was used for the assessment of the combination of daratumumab + lenalidomide + dexamethasone. With its written comments [3] and after the oral hearing [4], the company subsequently submitted further data on specific adverse events (AEs).

The CASTOR study was not used for the dossier assessment because it remained unclear whether the patients were treated in compliance with the approval [1]. As a result of the written comments [3] and the discussion in the oral hearing [4], however, the inclusion criteria of the CASTOR study were considered adequate and in line with the German health care context.

The G-BA commissioned IQWiG with the assessment of the CASTOR study under consideration of the information provided in the dossier. The commission additionally comprised the assessment of the data subsequently submitted by the company on specific AEs of the POLLUX study.

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.

Changes in comparison with Version 1.0

The present Version 1.1 of 1 February 2018 replaces Version 1.0 of the addendum of 26 January 2018. The following change is contained in Version 1.1 compared with Version 1.0:

- In the description of the results for the outcome "social functioning", the results were described as not statistically significant for both individual studies and the meta-analysis. Contrary to this description, the POLLUX study showed a statistically significant difference in favour of daratumumab, however. Since the results of the meta-analyses of the studies CASTOR and POLLUX were decisive for the benefit assessment, the textual descriptions of the results of the individual studies for all outcomes were deleted from Section 2.2.4 of the present Version 1.1.

The result of the assessment was not affected by this change.

2 Assessment

Research question 1 of the benefit assessment was the assessment of the added benefit of daratumumab in comparison with the appropriate comparator therapy (ACT) in patients with multiple myeloma who have received at least one prior therapy. For this research question, the company presented the studies POLLUX and CASTOR in its dossier.

Both studies were suitable for answering research question 1 of the benefit assessment. Patients with multiple myeloma with at least one prior therapy and documented progression after the last therapy were included in both studies. The POLLUX study compared daratumumab + lenalidomide + dexamethasone with lenalidomide + dexamethasone. The CASTOR study was a study on the comparison of daratumumab + bortezomib + dexamethasone with bortezomib + dexamethasone. Hence in both studies, daratumumab was used as add-on therapy in the intervention arm. Only one of the combination partners (lenalidomide or bortezomib) differed between the studies. Overall, both studies were considered sufficiently comparable, allowing a meta-analysis of the studies.

The present addendum has the following structure: Section 2.1 describes the characteristics of the CASTOR study. The characteristics of the POLLUX study were already described in dossier assessment A17-40 [1]. Sections 2.2 and 2.3 present the results and the derivation of the overall conclusion on the added benefit of daratumumab in research question 1 based on the studies POLLUX and CASTOR.

2.1 Characteristics of the CASTOR study

The CASTOR study is an ongoing, open-label randomized controlled trial (RCT) on the comparison of daratumumab + bortezomib + dexamethasone with bortezomib + dexamethasone in adults with multiple myeloma who have received at least one prior therapy and who have had documented progression after the last therapy.

According to the Summary of Product Characteristics (SPC), bortezomib is approved for patients with multiple myeloma who have received at least one prior therapy and who have already undergone or are unsuitable for haematopoietic stem cell transplantation (SCT) [5]. Before the start of the CASTOR study, about 61% of the patients included had received autologous SCT (ASCT) and were therefore candidates for treatment with bortezomib. For the remaining 39% of the patients included, it was not clear from the company's dossier whether and how many of these patients were actually unsuitable for SCT. Detailed reasons can be found in dossier assessment A17-40 [1].

As a result of the written comments [3] and the discussion in the oral hearing [4], however, the inclusion criteria of the CASTOR study were considered adequate and in line with the German health care context. The results of the CASTOR study are described and assessed below.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

A description of the characteristics of the study and of the interventions of the CASTOR study can be found in dossier assessment A17-40 [1].

Analysis and data cut-offs

Several analyses are planned in the CASTOR study. An interim analysis was conducted after about 80 patients had been treated for at least 8 weeks or had stopped their study treatment. Another interim analysis (first data cut-off from 11 January 2016) was conducted when 177 events of the primary outcome "progression-free survival (PFS)" were reached. Another analysis, which had not been prespecified by the company, was conducted in the framework of the 120-day safety update from 30 June 2016 required by the United States Food and Drug Administration (FDA) (second data cut-off) for the outcomes "PFS", "overall survival" and "safety". The CASTOR study is still ongoing. Another analyses is planned when 165 events of the outcome "overall survival" are reached. Section 2.2.2 describes for which data cut-off and for which outcomes data were available.

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 + dexamethasone vs. bortezomib + dexamethasone

Study **Outcome category** **Outcome**	**Planned follow-up observation**
CASTOR	
Mortality	
Overall survival	▪ Every 4 months until death
Morbidity	
Symptoms/health status	▪ EORTC QLQ-C30 (symptom scales)/EQ-5D VAS: week 8 and 16 after discontinuation of treatment or progression, start of a new antitumour treatment, or death
Health-related quality of life	▪ EORTC QLQ-C30 (functional scales): week 8 and 16 after discontinuation of treatment or until progression, start of a new antitumour treatment, or death
Side effects	
All outcomes in the category "side effects"	▪ Up to 30 days after the last dose of the study medication or until start of a new antitumour treatment

AE: adverse event; 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

For the outcome "overall survival", follow-up observation is planned until death. The observation periods for the outcomes "morbidity", "health-related quality of life" and "side effects" were systematically shortened because they were only recorded for the period of treatment with the study medication (plus 16 weeks for morbidity and health-related quality of life, and 30 days for side effects) or until the start of a new antitumour treatment (or until progression). To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to record these outcomes over the total period of time, as was the case for survival.

Characteristics of the study population

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

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

Study Characteristics Category	Daratumumab + bortezomib + dexamethasone	Bortezomib + dexamethasone
CASTOR	N[a] = 251	N[a] = 247
Age [years], mean (SD)	63 (10)	64 (10)
Sex [F/M], %	45/55	41/59
Ethnicity, n (%)		
Caucasian	216 (86.1)	219 (88.7)
Black/African American	14 (5.6)	6 (2.4)
Asian	12 (4.8)	11 (4.5)
Other[b]	11 (4.5)[c]	9 (3.9)[c]
ECOG PS, n (%)		
0	106 (42.4)	116 (47.0)
1	131 (52.4)	112 (45.3)
2	13 (5.2)	19 (7.7)
Myeloma type, n (%)		
IgG	136 (54.2)	148 (59.9)
IgA	59 (23.5)	54 (21.9)
IgM	1 (0.4)	1 (0.4)
IgD	6 (2.4)	3 (1.2)
IgE	0 (0)	0 (0)
FLC	43 (17.1)	36 (14.6)
FLC kappa	30 (12.0)	17 (6.9)
FLC lambda	13 (5.2)	19 (7.7)
Biclonal	2 (0.8)	3 (1.2)
Negative immune fixation	4 (1.6)	2 (0.8)

(continued)

Table 2: Characteristics of the study populations – RCT, direct comparison: daratumumab + bortezomib + dexamethasone vs. bortezomib + dexamethasone (continued)

Study Characteristics Category	Daratumumab + bortezomib + dexamethasone	Bortezomib + dexamethasone
CASTOR	N[a] = 251	N[a] = 247
ISS[d], n (%)		
I	98 (39.0)	96 (38.9)
II	94 (37.5)	100 (40.5)
III	59 (23.5)	51 (20.6)
Disease duration: time from first diagnosis of the multiple myeloma until randomization [years], mean (SD)	4.7 (3.2)	4.8 (3.3)
Prior therapies, n (%)	251 (100.0)	247 (100.0)
Prior systemic treatment	251 (100.0)	247 (100.0)
Prior ASCT	156 (62.2)	149 (60.3)
Prior radiotherapy	63 (25.1)	59 (23.9)
Number of prior therapies, n (%)		
1	122 (48.6)	113 (45.7)
2	70 (27.9)	74 (30.0)
3	37 (14.7)	32 (13.0)
> 3	22 (8.8)	28 (11.3)
Prior PI, n (%)	169 (67.3)	172 (69.6)
Bortezomib	162 (64.5)	164 (66.4)
Carfilzomib	12 (4.8)	10 (4.0)
Ixazomib	12 (4.8)	7 (2.8)
Prior IMiD, n (%)	179 (71.3)	198 (80.2)
Lenalidomide	89 (35.5)	120 (48.6)
Pomalidomide	7 (2.8)	7 (2.8)
Thalidomide	125 (49.8)	121 (49.0)
Treatment discontinuation, n (%)[e]	115 (47.3)	104 (43.9)
Study discontinuation, n (%)[f]	36 (14)	52 (21)

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: "Other" comprises the following groups; American Indian or native Alaskan, Hawaiian or Pacific, other, unknown, and not reported.
c: Institute's calculation.
d: ISS is based on the levels of serum beta 2 microglobulin and albumin.
e: Unclear whether the values refer to the discontinuation of all or of any of the treatment components.
f: Values refer to the first data cut-off (11 January 2016); data on the second data cut-off (30 June 2016) are not available.

ASCT: autologous stem cell transplantation; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; FLC: free light chains; IgA: immunoglobulin A; IgD: immunoglobulin D; IgE: immunoglobulin E; IgG: immunoglobulin G; IgM: immunoglobulin M; IMiD: immunomodulatory drug; ISS: International Staging System; M: male; n: number of patients in the category; N: number of randomized patients; PI: proteasome inhibitor; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The patient characteristics were largely comparable between the treatment groups of the CASTOR study. Most patients were white; the mean age was 64 years. According to the inclusion criteria, all patients had received at least one systemic treatment for multiple myeloma before study inclusion. About half of the patients were pretreated with 2 or more therapies. The majority of the patients included were allocated to International Staging System (ISS) stage I or II and had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1. About 61% of the patients had received prior ASCT. At the time point of the second data cut-off, 115 (about 47%) of the patients in the daratumumab arm had discontinued treatment; this was the case for 104 (about 44%) of the patients in the comparator arm. The treatment discontinuations were largely due to disease progression (about 33% of the patients in the daratumumab arm and about 25% in the comparator arm).

Course of the study

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

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

Study **Duration of the study phase** **Outcome category**	**Daratumumab + bortezomib + dexamethasone**	**Bortezomib + dexamethasone**
CASTOR	N = 251	N = 247
Treatment duration [months]		
First data cut-off: 11 January 2016		
Median [min; max]	6.44 [0.00; 14.78]	5.19 [0.00; 8.02]
Mean (SD)[a]	6.71 (3.02)	4.19 (1.69)
Second data cut-off: 30 June 2016		
Median [min; max]	11.07 [0.00; 21.22]	5.22 [0.00; 8.02]
Mean (SD)[a]	10.00 (4.73)	4.22 (1.70)
Observation period [months]		
Overall survival		
First data cut-off: 11 January 2016		
Median [95% CI]	7.49 [7.16; 8.21]	7.39 [6.93; 8.02]
Mean (SD)	7.50 (3.07)	7.29 (3.22)
Second data cut-off: 30 June 2016		
Median [95% CI]	13.01 [12.71; 13.70]	13.04 [12.55; 13.86]
Mean (SD)[a]	12.53 (4.07)	11.89 (4.43)
Morbidity, health-related quality of life, side effects	ND	ND

a: Referring to the safety population (243 vs. 237 patients).

Max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The differences in median treatment duration shown at the first data cut-off from 11 January 2016 (6.44 versus 5.19 months) increased notably until the second data cut-off from 30 June 2016: The median treatment duration was 11.07 months in the daratumumab arm versus 5.22 months in the comparator arm.

The median observation period for the outcome "overall survival" in the study arms was about the same at both data cut-offs. No information on the observation period was available for the outcomes of the categories "morbidity", "health-related quality of life" and "side effects". Due to the planned duration of the follow-up observation (see Table 1) and the differences in treatment duration and the time to progression, it can be assumed that there was a relevant difference in the observation periods for these outcomes between the study arms, however.

Risk of bias at study level

Table 4 shows the risk of bias at study level.

Table 4: Risk of bias at study level – RCT, direct comparison: daratumumab + bortezomib + dexamethasone vs. bortezomib + dexamethasone

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
CASTOR	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level for the CASTOR study was rated as low. This concurs with the company's assessment.

Limitations resulting from the open-label study design are described in Section 2.2.3 with the outcome-specific risk of bias.

2.2 Results on the added benefit based on the studies CASTOR and POLLUX

2.2.1 Data situation on specific adverse events in the POLLUX study

The G-BA commissioned IQWiG with the assessment of the data on specific AEs of the POLLUX study subsequently submitted by the company. For the POLLUX study, the company's dossier only contained analyses based on frequencies for the specific AEs chosen on the basis of the first data cut-off from 7 March 2016. With its comments [3], the company subsequently submitted survival time analyses of the specific AEs on the basis of the second data cut-off from 30 June 2016. These only included severe AEs (Common Terminology

Criteria for Adverse Events [CTCAE] grade ≥ 3), however. After the oral hearing [4], the company submitted further analyses on the side effects at the second data cut-off. These were survival time analyses of the System Organ Classes (SOCs) and Preferred Terms (PTs) of all severity grades. The presented PTs were not complete, however. It could therefore not be checked whether the choice of specific AEs conducted on the basis of AEs of the first data cut-off would change under consideration of the second data cut-off. The data on specific AEs subsequently submitted by the company are assessed below within the framework of a joint consideration of the studies CASTOR and POLLUX.

2.2.2 Outcomes included

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)
  - discontinuation due to AEs
  - severe AEs (CTCAE grade 3-4)
  - peripheral sensory neuropathy (PT)
  - febrile neutropenia (PT)
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A).

Table 5 shows for which outcomes data were available in the studies included.

Table 5: Matrix of outcomes – RCT, direct comparison: daratumumab arm vs. comparator arm

Study	Outcomes										
Time point	**Overall survival**	**Health status (EQ-5D VAS)**	**Symptoms (EORTC QLQ-C30 symptom scales)**	**Health-related quality of life (EORTC QLQ-C30 functional scales)**	**SAEs**	**Discontinuation due to AEs**	**Severe AEs (CTCAE grade 3–4)**	**Peripheral sensory neuropathy (PT)**	**Febrile neutropenia (PT)**	**Gastrointestinal disorders (SOC)**	**Respiratory, thoracic and mediastinal disorders (SOC)**
CASTOR[a]											
First data cut-off (11 Jan 2016)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Second data cut-off (30 Jun 2016)	Y	N[c]	N[c]	N[c]	Y	Y	Y	Y	Y	Y	Y
POLLUX[b]											
First data cut-off (7 Mar 2016)	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Second data cut-off (30 Jun 2016)	Y	N[c]	N[c]	N[c]	Y	Y[d]	Y	N	Y	N	N

a: The CASTOR study compared daratumumab + bortezomib + dexamethasone with bortezomib + dexamethasone.
b: The POLLUX study compared daratumumab + lenalidomide + dexamethasone with lenalidomide + dexamethasone.
c: No data available.
d: Data are available for discontinuation of all drug components, but not for discontinuation of any of the drug components.
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; 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; N: no; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus; Y: yes

The data available for the outcomes included were from different data cut-offs. The company presented results of the first data cut-offs for the outcomes on symptoms, health status and health-related quality of life, and results from the second data cut-offs for overall survival and side effects.

2.2.3 Risk of bias

Table 6 shows the risk of bias for the relevant outcomes in the relevant studies.

Table 6: Risk of bias at study and outcome level – RCT, direct comparison: daratumumab arm vs. comparator arm

Study	Study level	Outcomes										
		Overall survival	Health status (EQ-5D VAS)	Symptoms (EORTC QLQ-C30 symptom scales)	Health-related quality of life (EORTC QLQ-C30 functional scales)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade 3–4)	Peripheral sensory neuropathy (PT)	Febrile neutropenia (PT)	Gastrointestinal disorders (SOC)	Respiratory, thoracic and mediastinal disorders (SOC)
CASTOR[a]	L	L	H[c]	H[c]	H[c]	H[d]	H[c, d]	H[d]	H[d]	H[d]	H[d]	H[d]
POLLUX[b]	L	L	H[c]	H[c]	H[c]	H[d]	H[c, d]	H[d]	–[e]	H[d]	H[d]	H[d]

a: The CASTOR study compared daratumumab + bortezomib + dexamethasone with bortezomib + dexamethasone.
b: The POLLUX study compared daratumumab + lenalidomide + dexamethasone with lenalidomide + dexamethasone.
c: Lack of blinding in subjective recording of outcomes; in addition, except for discontinuation due to AEs: notable differences in the questionnaire return rate with potentially informative censoring.
d: Potentially informative censoring in treatment discontinuation due to progression (CASTOR: treatment discontinuation due to progression at the second data cut-off 33.3% [daratumumab + bortezomib + dexamethasone] and 25.3% [control], and median treatment durations until the second data cut-off 11.1 months [daratumumab + bortezomib + dexamethasone] and 5.2 months [control]) (POLLUX: treatment discontinuation due to progression at the first data cut-off: 14% [daratumumab + lenalidomide + dexamethasone] and 34% [control]) in connection with median treatment durations at the second data cut-off of 16.61 months [daratumumab + lenalidomide + dexamethasone] and 14.65 months [control]).
e: No data available
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; 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; H: high; L: low; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

The risk of bias of the outcome "overall survival" was rated as low in both studies. This concurs with the company's assessment.

The risk of bias in both studies was rated as high for the outcomes on health status (EQ-5D VAS), on symptoms and on health-related quality of life (EORTC QLQ-C30) due to a lack of blinding in subjective recording of outcomes and notable differences in the questionnaire return rate between both arms of the individual studies. The company also rated the risk of bias as high for these outcomes. In both studies, the risk of bias for the outcomes "SAEs", "severe

AEs" (CTCAE grade 3-4), "discontinuation due to AEs", and for the specific AEs was also rated as high due to potentially informative censoring. For the outcome "discontinuation due to AEs", there was additionally the lack of blinding. The company rated the risk of bias as high for all outcomes on side effects.

2.2.4 Results

Table 7 and Table 8 summarize the results of the comparison of daratumumab versus the ACT in adults with multiple myeloma who have received at least one prior therapy. Where necessary, Institute's own calculations are provided in addition to the data from the company's dossier. Fixed-effect models were chosen for the meta-analyses. With the exception of the respective concomitant and control treatment, the studies had a very similar design, and the reported effects were notably homogeneous for almost all the outcomes considered. The figures of the meta-analyses can be found in Appendix A. The Kaplan-Meier curve on overall survival in the CASTOR study can be found in Appendix B, and the results on common AEs in the CASTOR study are presented in Appendix C. The Kaplan-Meier curve and results on common AEs in the POLLUX study were already presented in dossier assessment A17-40 [1].

Table 7: Results (time to event) – RCT, direct comparison: daratumumab arm vs. comparator arm

Outcome category Study Outcome	Daratumumab arm N	Daratumumab arm Median time to event in months [95% CI] Patients with event n (%)	Comparator arm N	Comparator arm Median time to event in months [95% CI] Patients with event n (%)	Daratumumab arm vs. comparator arm HR [95% CI][a]; p-value
Mortality (second data cut-off 30 June 2016)					
Overall survival					
CASTOR[c]	251	NA 37 (14.7)	247	NA 58 (23.5)	0.63 [0.42; 0.96]; 0.029[b]
POLLUX[d]	286	NA 40 (14.0)	283	NA 56 (19.8)	0.63 [0.42; 0.95]; 0.027[b]
Total					0.63 [0.47; 0.84]; 0.002[e]
Morbidity (first data cut-off – CASTOR: 11 January 2016, POLLUX: 7 March 2016)					
Health status (EQ-5D VAS)					
Deterioration ≥ 7 points					
CASTOR[c]	251	2.8 [ND] 142 (56.6)	247	2.9 [ND] 136 (55.1)	1.00 [0.79; 1.28]; 0.981
POLLUX[d]	286	3.8 [ND] 170 (59.4)	283	3.7 [ND] 166 (58.7)	0.97 [0.78; 1.21]; 0.780
Total					0.98 [0.84; 1.16]; 0.841[e]
Deterioration ≥ 10 points					
CASTOR[c]	251	3.5 [ND] 127 (50.6)	247	3.5 [ND] 121 (49.0)	0.97 [0.75; 1.25]; 0.796
POLLUX[d]	286	4.9 [ND] 152 (53.1)	283	4.7 [ND] 149 (52.7)	0.97 [0.77; 1.21]; 0.759
Total					0.97 [0.82; 1.15]; 0.724[e]

(continued)

Table 7: Results (time to event) – RCT, direct comparison: daratumumab arm vs. comparator arm (continued)

Outcome category Study Outcome	Daratumumab arm N	Daratumumab arm Median time to event in months [95% CI] Patients with event n (%)	Comparator arm N	Comparator arm Median time to event in months [95% CI] Patients with event n (%)	Daratumumab arm vs. comparator arm HR [95% CI][a]; p-value[a]
Symptoms (EORTC QLQ-C30, deterioration ≥ 10 points)					
Fatigue					
CASTOR[c]	251	1.6 [ND] 166 (66.1)	247	2.1 [ND] 146 (59.1)	1.11 [0.88; 1.39]; 0.389
POLLUX[d]	286	1.9 [ND] 186 (65.0)	283	2.0 [ND] 181 (64.0)	1.11 [0.90; 1.36]; 0.341
Total					1.11 [0.95; 1.29]; 0.182[e]
Nausea/vomiting					
CASTOR[c]	251	7.3 [ND] 99 (39.4)	247	ND 74 (30.0)	1.22 [0.90; 1.66]; 0.195
POLLUX[d]	286	13.9 [ND] 117 (40.9)	283	10.3 [ND] 121 (42.8)	0.86 [0.66; 1.11]; 0.249
Total					1.0 [0.82; 1.21]; 0.966[e]
Pain					
CASTOR[c]	251	3.5 [ND] 141 (56.2)	247	3.7 [ND] 121 (49.0)	1.01 [0.79; 1.29]; 0.954
POLLUX[d]	286	5.6 [ND] 143 (50.0)	283	5.6 [ND] 159 (56.2)	0.89 [0.70; 1.11]; 0.298
Total					0.94 [0.80; 1.12]; 0.505[e]
Dyspnoea					
CASTOR[c]	251	3.5 [ND] 131 (52.2)	247	2.9 [ND] 125 (50.6)	0.93 [0.73; 1.19]; 0.571
POLLUX[d]	286	5.5 [ND] 152 (53.1)	283	5.7 [ND] 147 (51.9)	1.06 [0.84; 1.34]; 0.607
Total					1.00 [0.84; 1.18]; 0.961[e]

(continued)

Table 7: Results (time to event) – RCT, direct comparison: daratumumab arm vs. comparator arm (continued)

Outcome category Study Outcome	Daratumumab arm N	Daratumumab arm Median time to event in months [95% CI] Patients with event n (%)	Comparator arm N	Comparator arm Median time to event in months [95% CI] Patients with event n (%)	Daratumumab arm vs. comparator arm HR [95% CI][a]; p-value[a]
Insomnia					
CASTOR[c]	251	2.4 [ND] 134 (53.4)	247	2.9 [ND] 117 (47.4)	1.05 [0.81; 1.34]; 0.731
POLLUX[d]	286	6.6 [ND] 144 (50.3)	283	3.7 [ND] 157 (55.5)	0.80 [0.63; 1.00]; 0.052
Total					0.91 [0.76; 1.07]; 0.255[e]
Appetite loss					
CASTOR[c]	251	5.0 [ND] 119 (47.4)	247	5.9 [ND] 97 (39.3)	1.10 [0.83; 1.44]; 0.510
POLLUX[d]	286	7.2 [ND] 141 (49.3)	283	10.2 [ND] 128 (45.2)	1.08 [0.85; 1.38]; 0.536
Total					1.09 [0.90; 1.31]; 0.370[e]
Constipation					
CASTOR[c]	251	ND 99 (39.4)	247	7.3 [ND] 93 (37.7)	1.00 [0.75; 1.33]; 0.986
POLLUX[d]	286	4.7 [ND] 145 (50.7)	283	3.3 [ND] 157 (55.5)	0.87 [0.69; 1.10]; 0.242
Total					0.92 [0.77; 1.10]; 0.364[e]
Diarrhoea					
CASTOR[c]	251	5.7 [ND] 113 (45.0)	247	6.9 [ND] 90 (36.4)	1.12 [0.84; 1.49]; 0.436
POLLUX[d]	286	5.6 [ND] 159 (55.6)	283	5.7 [ND] 152 (53.7)	1.00 [0.79; 1.25]; 0.968
Total					1.05 [0.87; 1.25]; 0.628[e]

(continued)

Table 7: Results (time to event) – RCT, direct comparison: daratumumab arm vs. comparator arm (continued)

Outcome category Study Outcome	Daratumumab arm N	Daratumumab arm Median time to event in months [95% CI] Patients with event n (%)	Comparator arm N	Comparator arm Median time to event in months [95% CI] Patients with event n (%)	Daratumumab arm vs. comparator arm HR [95% CI][a]; p-value[a]
Health-related quality of life (first data cut-off – CASTOR: 11 January 2016, POLLUX: 7 March 2016)					
EORTC QLQ-C30 functional scales (deterioration ≥ 10 points)					
General health status					
CASTOR[c]	251	3.5 [ND] 123 (49.0)	247	3.7 [ND] 122 (49.4)	0.94 [0.73; 1.21]; 0.625
POLLUX[d]	286	4.7 [ND] 153 (53.5)	283	4.7 [ND] 155 (54.8)	0.96 [0.76; 1.20];0.701
Total					0.95 [0.80; 1.13]; 0.561[e]
Physical functioning					
CASTOR[c]	251	4.3 [ND] 129 (51.4)	247	4.2 [ND] 118 (47.8)	0.93 [0.72; 1.20]; 0.576
POLLUX[d]	286	5.9 [ND] 147 (51.4)	283	7.5 [ND] 136 (48.1)	1.09 [0.86; 1.38]; 0.484
Total					1.01 [0.85; 1.20]; 0.884[e]
Role functioning					
CASTOR[c]	251	2.3 [ND] 152 (60.6)	247	2.8 [ND] 133 (53.8)	1.17 [0.93; 1.49]; 0.188
POLLUX[d]	286	3.7 [ND] 171 (59.8)	283	3.1 [ND] 169 (59.7)	0.92 [0.74; 1.14]; 0.446
Total					1.03 [0.88; 1.20]; 0.745[e]
Emotional functioning					
CASTOR[c]	251	5.7 [ND] 113 (45.0)	247	4.4 [ND] 113 (45.7)	0.82 [0.63; 1.08]; 0.151
POLLUX[d]	286	6.6 [ND] 136 (47.6)	283	7.8 [ND] 134 (47.3)	1.04 [0.82; 1.32]; 0.753
Total					0.94 [0.78; 1.12]; 0.476[e]

(continued)

Table 7: Results (time to event) – RCT, direct comparison: daratumumab arm vs. comparator arm (continued)

Outcome category Study Outcome	Daratumumab arm N	Daratumumab arm Median time to event in months [95% CI] Patients with event n (%)	Comparator arm N	Comparator arm Median time to event in months [95% CI] Patients with event n (%)	Daratumumab arm vs. comparator arm HR [95% CI][a]; p-value[a]
Social functioning					
CASTOR[c]	251	3.0 [ND] 152 (60.6)	247	3.0 [ND] 129 (52.2)	1.11 [0.87; 1.41]; 0.390
POLLUX[d]	286	3.8 [ND] 161 (56.3)	283	2.9 [ND] 175 (61.8)	0.80 [0.64; 0.995]; 0.045
Total					0.93 [0.79; 1.09]; 0.373[e]
Cognitive functioning					
CASTOR[c]	251	3.5 [ND] 142 (56.6)	247	3.4 [ND] 125 (50.6)	0.95 [0.74; 1.22]; 0.690
POLLUX[d]	286	4.9 [ND] 159 (55.6)	283	4.6 [ND] 162 (57.2)	0.93 [0.74; 1.16]; 0.505
Total					0.94 [0.79; 1.11]; 0.460

a: Hazard ratio (including 95% CI) calculated using Cox proportional hazards model with treatment as sole explanatory variable and stratified by the factors ISS (I, II or III), number of prior therapies (1 vs. 2 or 3 vs. > 3) and prior therapy with bortezomib or lenalidomide (no vs. yes).
b: p-value calculated using log-rank test stratified by the factors ISS (I, II or III), number of prior therapies (1 vs. 2 or 3 vs. > 3) and prior therapy with bortezomib (no vs. yes).
c: The CASTOR study compared daratumumab + bortezomib + dexamethasone with bortezomib + dexamethasone.
d: The POLLUX study compared daratumumab + lenalidomide + dexamethasone with lenalidomide + dexamethasone.
e: Institute's calculation.

AE: adverse event; 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; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; ISS: International Staging System; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Table 8: Results (side effects) (time to event) – RCT, direct comparison: daratumumab arm vs. comparator arm

Outcome category Outcome Study	Daratumumab arm N	Daratumumab arm Median time to event in months [95% CI] Patients with event n (%)	Comparator arm N	Comparator arm Median time to event in months [95% CI] Patients with event n (%)	Daratumumab arm vs. comparator arm HR [95% CI][a]; p-value
Side effects (second data cut-off 30 June 2016)					
AEs					
CASTOR[b]	243	ND 240 (98.8)	237	ND 226 (95.4)	–
POLLUX[c]	283	ND 279 (98.6)	281	ND 274 (97.5)	–
SAEs					
CASTOR[b]	243	14.1 [ND] 118 (48.6)	237	NA [ND] 81 (34.2)	1.24[d] [0.92; 1.65]; 0.153
POLLUX[c]	283	14.3 [ND] 153 (54.1)	281	16.8 [ND] 126 (44.8)	1.14[d] [0.90; 1.44]; 0.290
Total					1.18 [0.98; 1.42]; 0.079[e]
Discontinuation due to AEs (of all drug components)					
CASTOR[b]	243	– 22 (9.1)	237	– 22 (9.3)	RR: 0.98 [0.56; 1.71]; > 0.999[f]
POLLUX[c]	283	– 24 (8.5)	281	NA 24 (8.5)	RR: 0.99 [0.58; 1.71]; > 0.999[f]
Total					0.98 [0.67; 1.45]; 0.937[e]
Discontinuation due to AEs (of any drug component)					
CASTOR[b]	243	– 40 (16.5)	237	– 39 (16.5)	RR: 1.00 [0.67; 1.50][g]; > 0.999[f]
POLLUX[c]	No data available				
Total					

(continued)

Table 8: Results (side effects) (time to event) – RCT, direct comparison: daratumumab arm vs. comparator arm (continued)

Outcome category Outcome Study	Daratumumab arm N	Daratumumab arm Median time to event in months [95% CI] Patients with event n (%)	Comparator arm N	Comparator arm Median time to event in months [95% CI] Patients with event n (%)	Daratumumab arm vs. comparator arm HR [95% CI][a]; p-value[a]
Severe AEs (CTCAE grade 3–4)					
CASTOR[b]	243	1.2 [ND] 193 (79.4)	237	1.9 [ND] 149 (62.9)	1.42[d] [1.14; 1.77]; 0.002
POLLUX[c]	283	1.0 [ND] 235 (83.0)	281	3.4 [ND] 210 (74.7)	1.39 [1.15; 1.68]; < 0.001
Total					1.40 [1.22; 1.62]; < 0.001[e]
Specific adverse events					
Febrile neutropenia					
CASTOR[b]	243	ND 4 (1.6)	237	ND 1 (0.4)	3.93 [0.44; 35.24]; 0.221
POLLUX[c]	283	ND 16 (5.7)	281	ND 7 (2.5)	2.11 [0.87; 5.13]; 0.100
Total					2.30 [1.01; 5.25]; 0.047[e]
Peripheral sensory neuropathy					
CASTOR[b]	243	5.6 [ND] 120 (49.4)	237	7.5 [ND] 90 (38.0)	1.18[d] [0.89; 1.55]; 0.251
POLLUX[c]	No data available				
Gastrointestinal disorders					
CASTOR[b]	243	3.75 [ND] 155 (63.8)	237	ND 111 (46.8)	1.38 [1.08; 1.77]; 0.012
POLLUX[c]	283	1.28 [ND] 220 (77.7)	281	6.37 [ND] 174 (61.9)	1.59 [1.29; 1.94]; < 0.001
Total					1.50 [1.28; 1.76]; < 0.001[e]
Respiratory, thoracic and mediastinal disorders					
CASTOR[b]	243	3.5 [ND] 137 (56.4)	237	ND 78 (32.9)	2.12 [1.58; 2.84]; < 0.001
POLLUX[c]	283	2.56 [ND] 176 (62.2)	281	ND 118 (42.0)	1.94 [1.52; 2.47]; < 0.001
Total					2.01 [1.67; 2.42]; < 0.001[e]

(continued)

Table 8: Results (side effects) (time to event) – RCT, direct comparison: daratumumab arm vs. comparator arm (continued)

a: Hazard ratio (including 95% CI) calculated using Cox proportional hazards model with treatment as sole explanatory variable and stratified by the factors ISS (I, II or III), number of prior therapies (1 vs. 2 or 3 vs. > 3) and prior therapy with bortezomib or lenalidomide (no vs. yes).
b: The CASTOR study compared daratumumab + bortezomib + dexamethasone with bortezomib + dexamethasone.
c: The POLLUX study compared daratumumab + lenalidomide + dexamethasone with lenalidomide + dexamethasone.
d: Hazard ratio (including 95% CI and p-value) calculated using Cox proportional hazards model without consideration of the stratification factors.
e: Institute's calculation (meta-analysis: fixed-effect model).
f: Institute's calculation, unconditional exact test (CSZ method according to [6]).
g: Institute's calculation, asymptotic.
AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; 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; HR: hazard ratio; ISS: International Staging System; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

In principle, it is possible to derive proof, e.g. of an added benefit of daratumumab, based on the meta-analysis of 2 studies with a low risk of bias across the outcomes.

Mortality

Overall survival

The meta-analysis showed a statistically significant difference in favour of daratumumab between the treatment groups for the outcome "overall survival". As a result, there was proof of an added benefit of daratumumab in comparison with the ACT.

Morbidity

Health status (EQ-5D VAS)

The outcome "health status" was recorded with the EQ-5D VAS. The meta-analysis showed no statistically significant difference between the treatment groups. Overall, this resulted in no hint of an added benefit of daratumumab in comparison with the ACT for the outcome "health status"; an added benefit is therefore not proven.

Symptoms (EORTC QLQ-C30)

Symptom outcomes were recorded using the EORTC QLQ-C30 symptom scales.

The meta-analysis showed no statistically significant difference between the treatment groups for each of the following outcomes: fatigue, nausea and vomiting, pain, dyspnoea, insomnia, loss of appetite, constipation and diarrhoea. This resulted in no hint of an added benefit of daratumumab in comparison with the ACT for these outcomes; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life was recorded with the EORTC QLQ-C30 functional scales.

The meta-analysis showed no statistically significant difference between the treatment groups for each of the following outcomes: general health status, physical functioning, role functioning, emotional functioning, and cognitive functioning. This resulted in no hint of an added benefit of daratumumab in comparison with the ACT for these outcomes; an added benefit is therefore not proven.

Side effects

Serious adverse events, discontinuation due to adverse events

The meta-analysis showed no statistically significant difference between the treatment groups for the outcomes "SAEs" and "discontinuation due to AEs" (both of all drug components and of any of the drug components). Hence, there was no hint of greater or lesser harm from daratumumab in comparison with the ACT for any of these outcomes; greater or lesser harm is therefore not proven for these outcomes.

Severe adverse events (CTCAE grade 3–4)

The meta-analysis showed a statistically significant difference to the disadvantage of daratumumab in comparison with the ACT for the outcome "severe AEs (CTCAE grade 3-4)". The risk of bias for the outcome was rated as high in both studies. Nonetheless, a high certainty of results was assumed for the CASTOR study because most events on this outcome occurred very early in the course of the study. In contrast, treatment discontinuations due to progression of the underlying disease occurred to a relevant degree only much later in the course of the study (see Figure 25 and Figure 26). The effect was mainly determined by the early events and not put into question by the progression events occurring later. As a result, there was proof of greater harm of daratumumab in comparison with the ACT.

Specific adverse events

The meta-analysis showed no statistically significant difference between the treatment groups for the outcomes "febrile neutropenia" and "peripheral sensory neuropathy". Hence, there was no hint of greater or lesser harm from daratumumab in comparison with the ACT for any of these outcomes; greater or lesser harm is therefore not proven for these outcomes.

The meta-analysis showed a statistically significant difference to the disadvantage of daratumumab in comparison with the ACT for the outcomes "gastrointestinal disorders" and "respiratory, thoracic and mediastinal disorders". Both outcomes had a high risk of bias. As a result, there was an indication of greater harm of daratumumab in comparison with the ACT.

2.2.5 Subgroups and other effect modifiers

The following subgroup characteristics were considered to be relevant for the present benefit assessment:

- sex (men/women)
- age (< 65/≥ 65 years)
- ethnicity (Caucasian/Asian/other)
- ISS stage (stage I/stage II/stage III)
- number of prior therapies

Both studies showed inconsistent results on effect modifications, which is why meta-analyses of both studies were required. The company did not present interaction tests based on meta-analyses of the studies POLLUX and CASTOR in its dossier. Subgroup results could therefore not be used for the present assessment.

2.3 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below. The various outcome categories and the effect sizes are taken into account. The methods used for this purpose are explained in the *General Methods* of IQWiG [7].

2.3.1 Assessment of the added benefit at outcome level

Based on the results presented in Section 2.2, the extent of the respective added benefit at outcome level is estimated in the following Table 9.

Table 9: Extent of added benefit at outcome level: daratumumab in combination with bortezomib + dexamethasone or lenalidomide + dexamethasone vs. ACT

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Intervention vs. comparator** **Median time to event or proportion of events** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality (second data cut-off 30 June 2016)		
Overall survival	Median: NA vs. NA months HR: 0.63 [0.47; 0.84]; p = 0.002 probability: "proof"	Outcome category: "mortality" $CI_u < 0.85$ added benefit, extent: "major"
Morbidity (first data cut-off: 11 January 2016)		
Health status (EQ-5D VAS)		
Deterioration ≥ 7 points	Median: 2.8–3.8 vs. 2.9–3.7[c] months HR: 0.98 [0.84; 1.16]; p = 0.841	Lesser benefit/added benefit not proven
Deterioration ≥ 10 points	Median: 3.5–4.9 vs. 3.5–4.7[c] months HR: 0.97 [0.82; 1.15]; p = 0.724	
Symptoms (EORTC QLQ-C30, deterioration ≥ 10 points)		
Fatigue	Median: 1.6–1.9 vs. 2.0–2.1[c] months HR: 1.11 [0.95; 1.29]; p = 0.182	Lesser benefit/added benefit not proven
Nausea/vomiting	Median: 7.3–13.9 vs. ND–10.3[c] months HR: 1.0 [0.82; 1.21]; p = 0.966	Lesser benefit/added benefit not proven
Pain	Median: 3.5–5.6 vs. 3.7–5.6[c] months HR: 0.94 [0.80; 1.12]; p = 0.505	Lesser benefit/added benefit not proven
Dyspnoea	Median: 3.5–5.5 vs. 2.9–5.7[c] months HR: 1.00 [0.84; 1.18]; p = 0.961	Lesser benefit/added benefit not proven
Insomnia	Median: 2.4–6.6 vs. 2.9–3.7[c] months HR: 0.91 [0.76; 1.07]; p = 0.255	Lesser benefit/added benefit not proven
Appetite loss	Median: 5.0–7.2 vs. 5.9–10.2[c] months HR: 1.09 [0.90; 1.31]; p = 0.370	Lesser benefit/added benefit not proven
Constipation	Median: ND–4.7 vs. 3.3–7.3[c] months HR: 0.92 [0.77; 1.10]; p = 0.364	Lesser benefit/added benefit not proven
Diarrhoea	Median: 5.6–5.7 vs. 5.7–6.9[c] months HR: 1.05 [0.87; 1.25]; p = 0.628	Lesser benefit/added benefit not proven
Health-related quality of life (first data cut-off: 11 January 2016)		
EORTC QLQ-C30 functional scales (deterioration ≥ 10 points)		
General health status	Median: 3.5–4.7 vs. 3.7–4.7[c] months HR: 0.95 [0.80; 1.13]; p = 0.561	Lesser benefit/added benefit not proven
Physical functioning	Median: 4.3–5.9 vs. 4.2–7.5[c] months HR: 1.01 [0.85; 1.20]; p = 0.884	Lesser benefit/added benefit not proven
Role functioning	Median: 2.3–3.7 vs. 2.8–3.1[c] months HR: 1.03 [0.88; 1.20]; p = 0.745	Lesser benefit/added benefit not proven
Emotional functioning	Median: 5.7–6.6 vs. 4.4–7.8[c] months HR: 0.94 [0.78; 1.12]; p = 0.476	Lesser benefit/added benefit not proven

(continued)

Table 9: Extent of added benefit at outcome level: daratumumab in combination with bortezomib + dexamethasone or lenalidomide + dexamethasone vs. ACT (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Intervention vs. comparator** **Median time to event or proportion of events** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Social functioning	Median: 3.0–3.8 vs. 2.9–3.0[c] months HR: 0.93 [0.79; 1.09]; p = 0.373	Lesser benefit/added benefit not proven
Cognitive functioning	Median: 3.5–4.9 vs. 3.4–4.6[c] months HR: 0.94 [0.79; 1.11]; p = 0.460	Lesser benefit/added benefit not proven
Side effects		
SAEs	Median: 14.1–14.3 vs. ND–16.8[c] months HR: 1.18 [0.98; 1.42]; p = 0.079	Greater/lesser harm not proven
Discontinuation due to AEs (of all drug components)	8.5–9.1% vs. 8.5–9.3%[c] RR: 0.98 [0.67; 1.45]; p = 0.937	Greater/lesser harm not proven
Discontinuation due to AEs (of any drug component)	16.5% vs. 16.5% RR: 1.00 [0.67; 1.50]; p > 0.999[d]	
Severe AEs (CTCAE grade 3–4)	Median: 1.0–1.2 vs. 1.9–3.4[c] months HR: 1.40 [1.22; 1.62]; p < 0.001 HR: 0.71 [0.62; 0.82][e] probability: "proof"	Outcome category: serious/severe side effects $0.75 < CI_u \leq 0.9$ greater harm, extent: "considerable"
Febrile neutropenia	Median: ND vs. ND months HR: 2.30 [1.01; 5.25]; p = 0.047 HR: 0.53 [0.19; 0.99][e] Probability: "indication"	Outcome category: non-serious/non-severe side effects $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[f]
Peripheral sensory neuropathy	Median: 5.6 vs. 7.5 months HR: 1.18 [0.89; 1.55]; p = 0.251[d]	Greater/lesser harm not proven
Gastrointestinal disorders	Median: 1.28–3.75 vs. ND–6.37[c] months HR: 1.50 [1.28; 1.76]; p < 0.001 HR: 0.67 [0.57; 0.78][e] Probability: "indication"	Outcome category: non-serious/non-severe side effects $CI_u < 0.8$ greater harm, extent: "considerable"
Respiratory, thoracic and mediastinal disorders	Median: 2.56–3.5 vs. ND–ND[c] months HR: 2.01 [1.67; 2.42]; p < 0.001 HR: 0.50 [0.41; 0.60] Probability: "indication"	Outcome category: non-serious/non-severe side effects $CI_u < 0.8$ greater harm, extent: "considerable"

a: Probability provided if a statistically significant and relevant effect is present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Minimum and maximum proportions of events in each treatment arm in the studies included.
d: The result is based on only one study.
e: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
f: The extent of the effect in this non-serious/non-severe outcome was no more than marginal.

(continued)

Table 9: Extent of added benefit at outcome level: daratumumab in combination with bortezomib + dexamethasone or lenalidomide + dexamethasone vs. ACT (continued)

AE: adverse event; CI: confidence interval; CI_u: upper limit of 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; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; ISS: International Staging System; NA: not achieved; ND: no data; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.3.2 Overall conclusion on added benefit

Table 10 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 10: Positive and negative effects from the assessment of daratumumab in combination with bortezomib + dexamethasone or lenalidomide + dexamethasone vs. ACT

Positive effects	**Negative effects**
Mortality ▪ Overall survival: proof of an added benefit – extent: “major”	–
–	Serious/severe side effects ▪ severe AEs (CTCAE grade 3–4): proof of greater harm – extent “considerable”
–	Non-serious/non-severe side effects: ▪ gastrointestinal disorders: indication of greater harm – extent: “considerable” ▪ respiratory, thoracic and mediastinal disorders: indication of greater harm – extent: “considerable”
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; vs.: versus	

The overall assessment showed, on the side of positive effects, proof of major added benefit for the outcome “overall survival”. In contrast, there was 1 proof and 2 indications of greater harm, each with the extent “considerable”, on the side of negative effects. In the overall assessment, the extent of the added benefit was reduced by the negative effects. In summary, there is proof of considerable added benefit of daratumumab in combination with bortezomib + dexamethasone or lenalidomide + dexamethasone versus bortezomib + dexamethasone or lenalidomide + dexamethasone for patients with multiple myeloma who have received at least one prior therapy.

2.3.3 List of included studies

Study CASTOR

Janssen Research & Development (2014). Phase 3 study comparing daratumumab, bortezomib and dexamethasone (DVd) vs bortezomib and dexamethasone (Vd) in subjects with relapsed or refractory multiple myeloma: study 54767414MMY3004; clinical protocol [unpublished].

Janssen Research & Development (2016). Daratumumab treatment for patients with multiple myeloma who received at least one prior therapy: 120-day safety update [unpublished].

Janssen Research & Development (2016). Phase 3 study comparing daratumumab, bortezomib, and dexamethasone (DVd) vs bortezomib and dexamethasone (Vd) in subjects with relapsed or refractory multiple myeloma: study 54767414MMY3004; clinical study report [unpublished].

Janssen Research & Development (2016). Phase 3 study comparing daratumumab, bortezomib, and dexamethasone (DVd) vs bortezomib and dexamethasone (Vd) in subjects with relapsed or refractory multiple myeloma: study 54767414MMY3004; documentation of statistical methods and interim analysis plans [unpublished].

Janssen Research & Development (2017, 13.12.2017). "Addition of daratumumab to combination of bortezomib and dexamethasone in participants with relapsed or refractory multiple myeloma: study details." from https://ClinicalTrials.gov/show/NCT02136134. Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: No masking|Primary Purpose: Treatment

Janssen-Cilag (2017). Zusatzanalysen der Studien 54767414MMY3003 POLLUX und 54767414MMY3004 CASTOR [unpublished].

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Study POLLUX

See dossier assessment A17-40 [1].

3 Summary

The assessment of the CASTOR study and the meta-analysis of the studies CASTOR and POLLUX changed the conclusion on the added benefit of daratumumab from dossier assessment A17-40 [1] in research question 1. The following Table 11 shows the result of the benefit assessment of daratumumab under consideration of dossier assessment A17-40 [1] and the present addendum.

Table 11: Daratumumab – probability and extent of added benefit

Research question	**Subindication**	**ACT[a]**	**Probability and extent of added benefit[b]**
1	Daratumumab in combination with lenalidomide and dexamethasone, or in combination with bortezomib and dexamethasone: adult patients with multiple myeloma who have received at least one prior therapy[c]	Bortezomib in combination with pegylated liposomal doxorubicin or **bortezomib in combination with dexamethasone** or **lenalidomide in combination with dexamethasone** or elotuzumab in combination with lenalidomide and dexamethasone	**Proof of considerable added benefit**
2	Daratumumab as monotherapy: adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a PI and an IMiD, and who have demonstrated disease progression on the last therapy[d]	Individual treatment specified by the physician under consideration of prior therapies, duration and extent of the response, and the approval of the drugs[e]	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: Changes in comparison with dossier assessment A17-40 are printed in bold.
c: It is assumed for the present therapeutic indication that the use of daratumumab in combination with lenalidomide and dexamethasone, or in combination with bortezomib and dexamethasone, is conducted in the framework of a remission-inducing induction treatment. High-dose chemotherapy with stem cell transplantation, which may be a subsequent treatment option, is therefore not an option as part of the ACT.
d: It is assumed for the present therapeutic indication that high-dose chemotherapy with stem cell transplantation is not an option at the time point of the current treatment.
e: This also includes BSC, which ensures best possible supportive therapy, optimized for the individual patient, for alleviation of symptoms and improvement in the quality of life.
ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; IMiD: immunomodulatory drug; PI: proteasome inhibitor

The G-BA decides on the added benefit.

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Appendix A – Figures of the meta-analyses

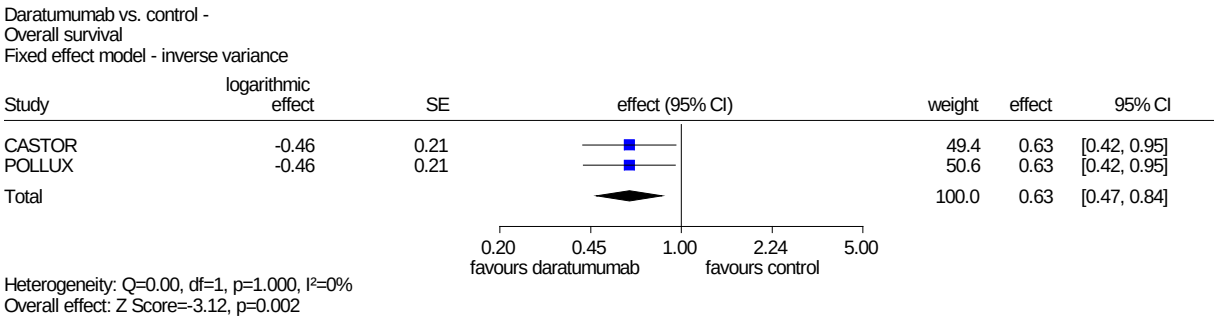

Figure 1: Meta-analysis, all-cause mortality, daratumumab vs. control; effect estimate: HR

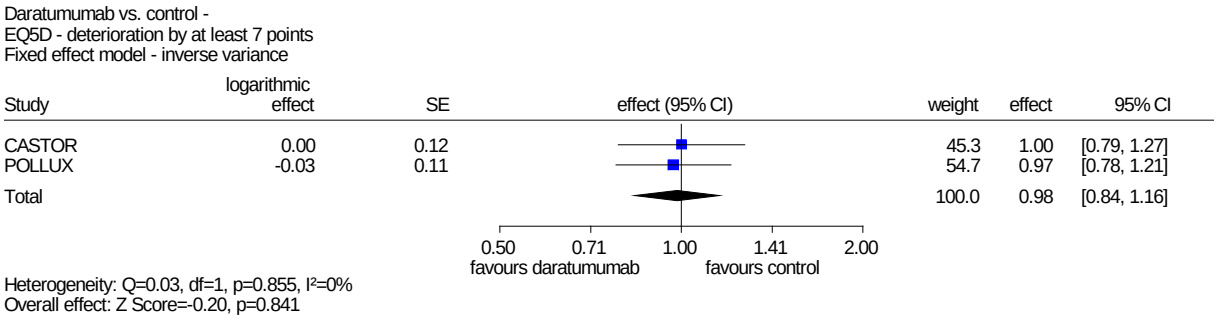

Figure 2: Meta-analysis, health status (EQ-5D VAS), deterioration by at least 7 points, daratumumab vs. control; effect estimate: HR

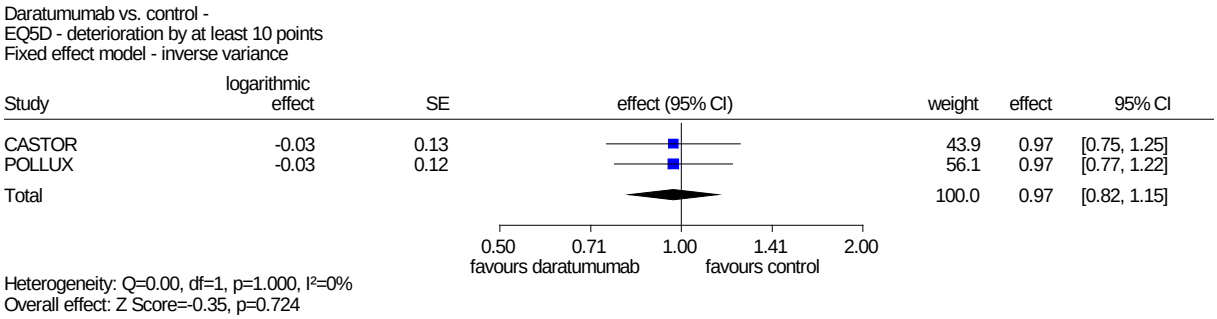

Figure 3: Meta-analysis, health status (EQ-5D VAS), deterioration by at least 10 points, daratumumab vs. control; effect estimate: HR

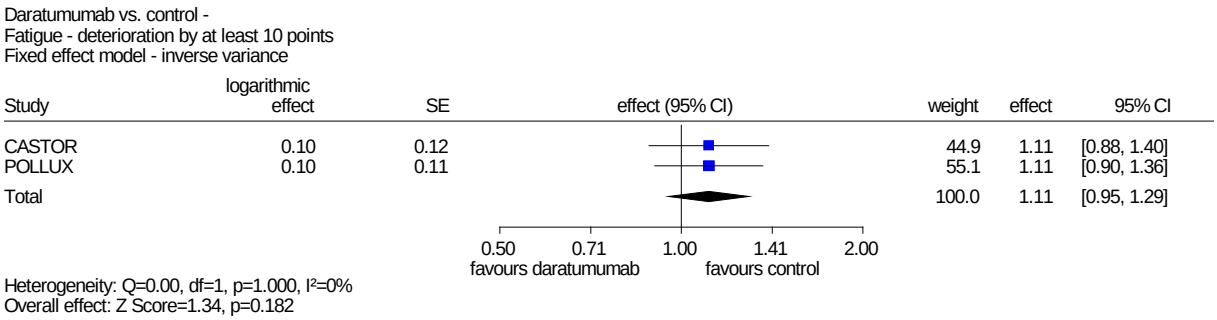

Figure 4: Meta-analysis, symptoms: fatigue, deterioration by at least 10 points, daratumumab vs. control; effect estimate: HR

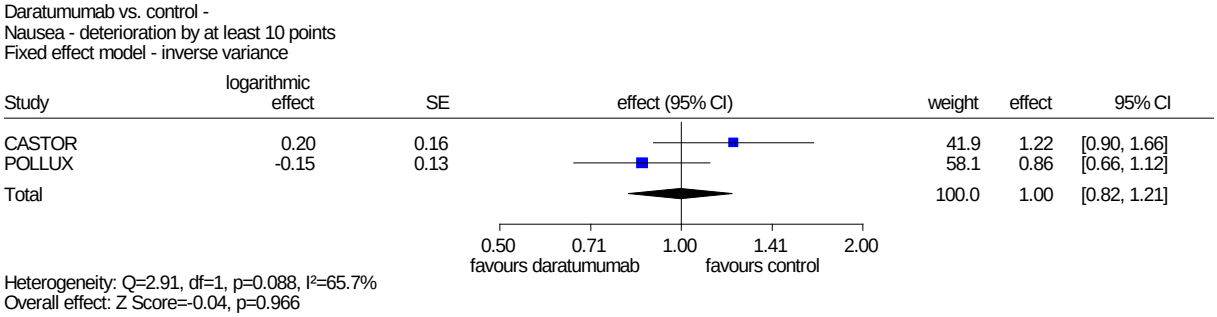

Figure 5: Meta-analysis, symptoms: nausea and vomiting, deterioration by at least 10 points, daratumumab vs. control; effect estimate: HR

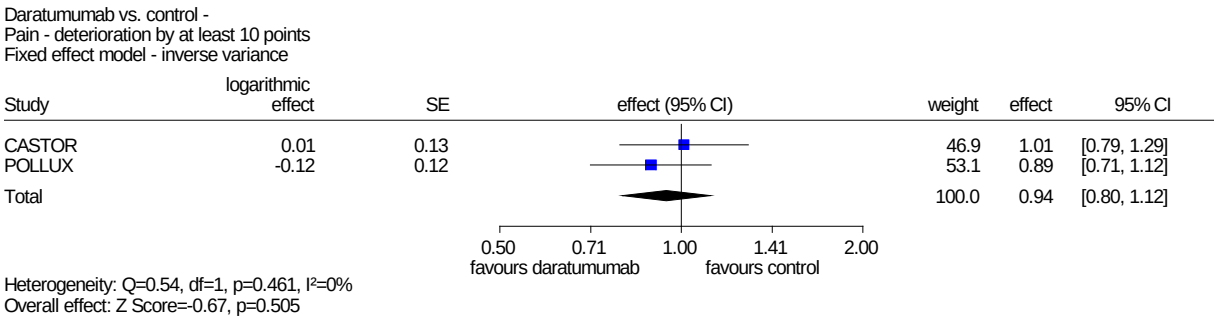

Figure 6: Meta-analysis, symptoms: pain, deterioration by at least 10 points, daratumumab vs. control; effect estimate: HR

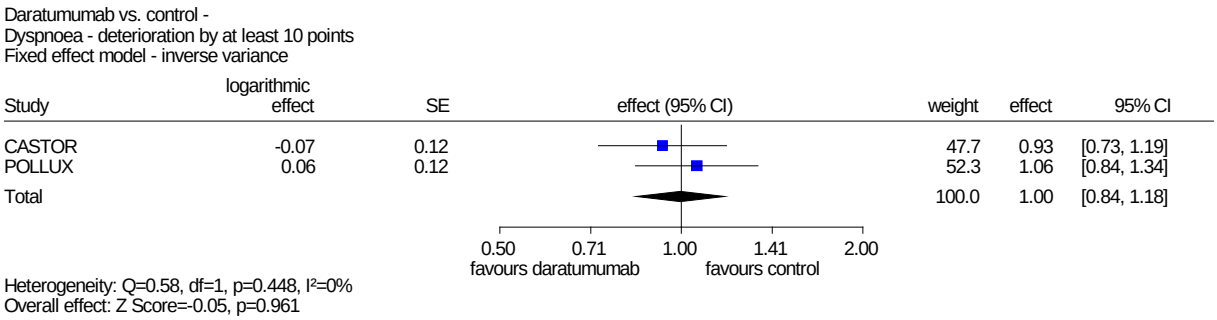

Figure 7: Meta-analysis, symptoms: dyspnoea, deterioration by at least 10 points, daratumumab vs. control; effect estimate: HR

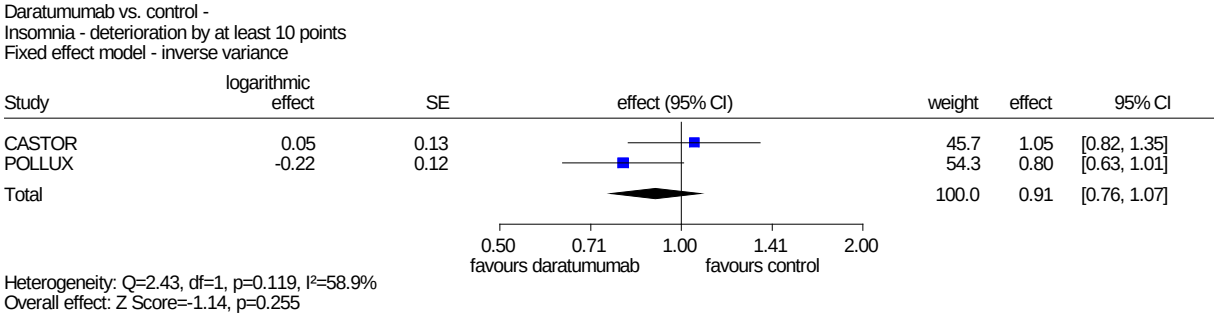

Figure 8: Meta-analysis, symptoms: insomnia, deterioration by at least 10 points, daratumumab vs. control; effect estimate: HR

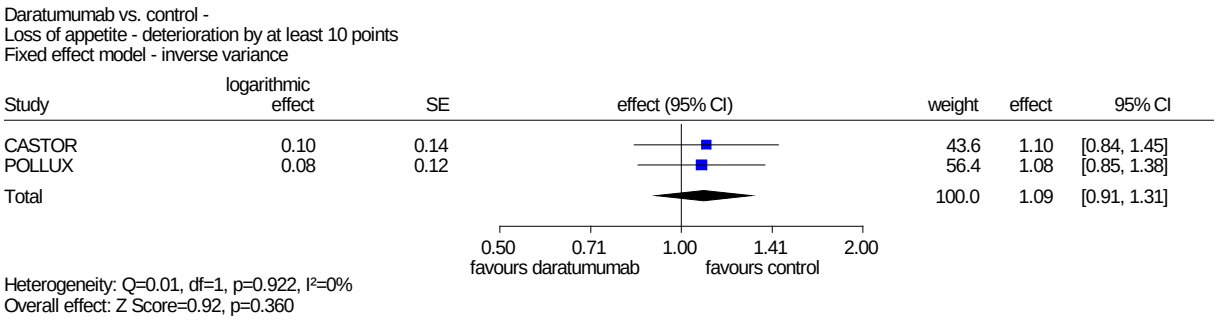

Figure 9: Meta-analysis, symptoms: loss of appetite, deterioration by at least 10 points, daratumumab vs. control; effect estimate: HR

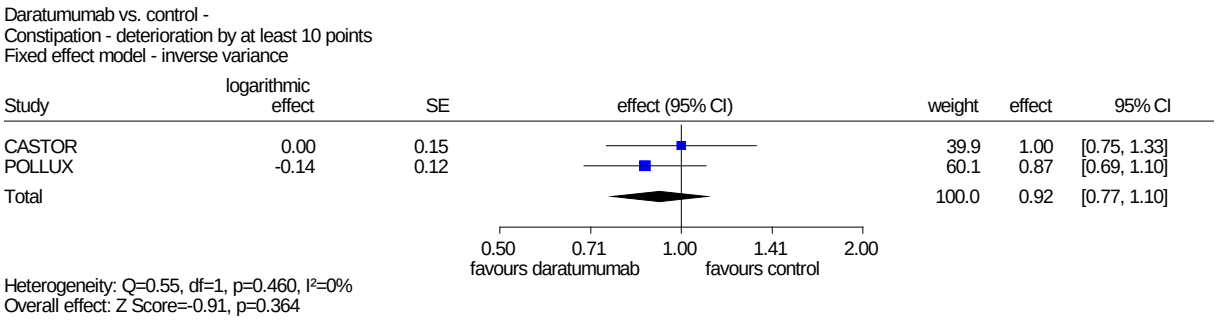

Figure 10: Meta-analysis, symptoms: constipation, deterioration by at least 10 points, daratumumab vs. control; effect estimate: HR

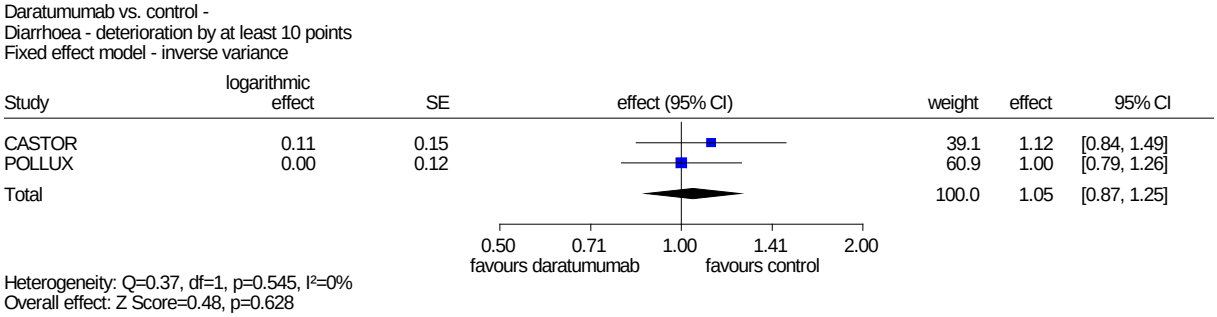

Figure 11: Meta-analysis, symptoms: diarrhoea, deterioration by at least 10 points, daratumumab vs. control; effect estimate: HR

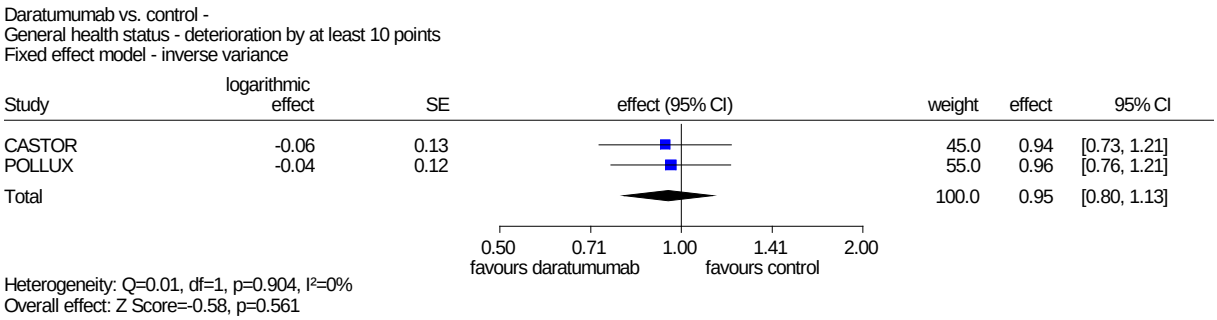

Figure 12: Meta-analysis, health-related quality of life: general health status, deterioration by at least 10 points, daratumumab vs. control; effect estimate: HR

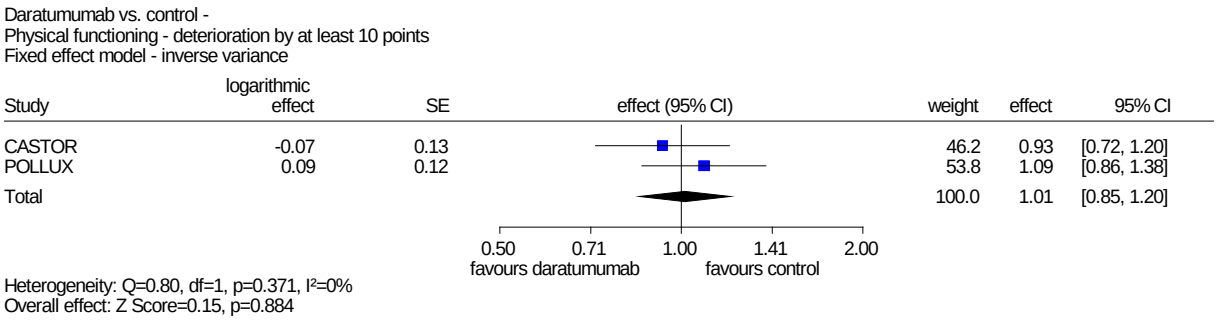

Figure 13: Meta-analysis, health-related quality of life: physical functioning, deterioration by at least 10 points, daratumumab vs. control; effect estimate: HR

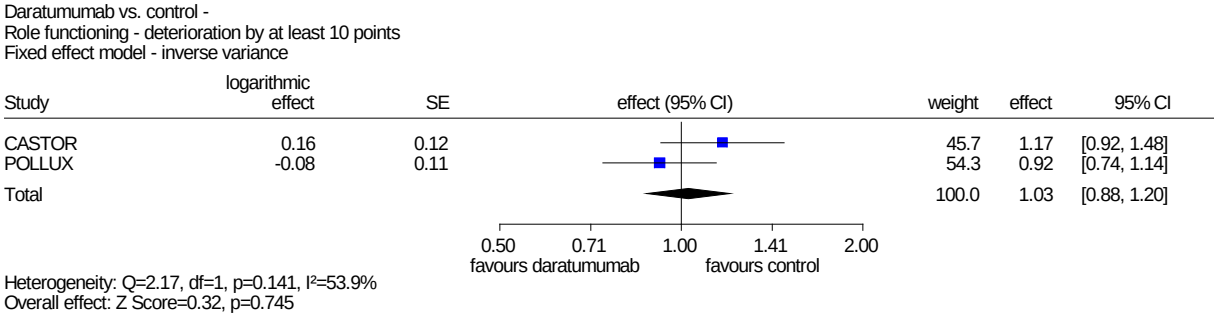

Figure 14: Meta-analysis, health-related quality of life: role functioning, deterioration by at least 10 points, daratumumab vs. control; effect estimate: HR

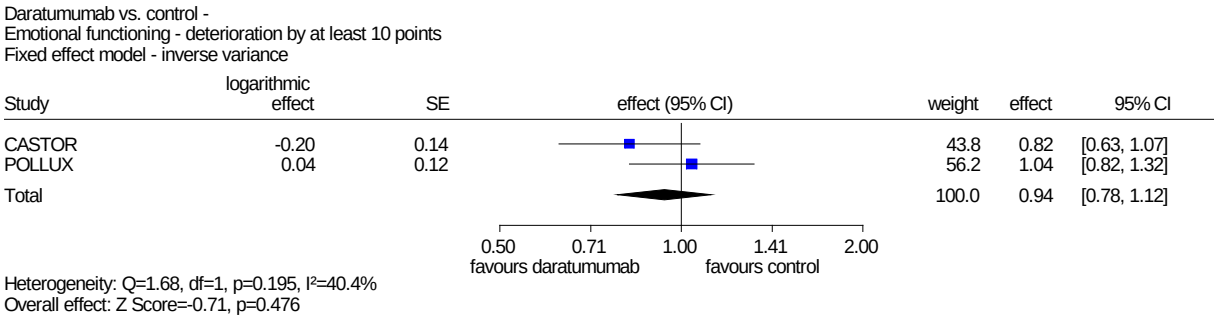

Figure 15: Meta-analysis, health-related quality of life: emotional functioning, deterioration by at least 10 points, daratumumab vs. control; effect estimate: HR

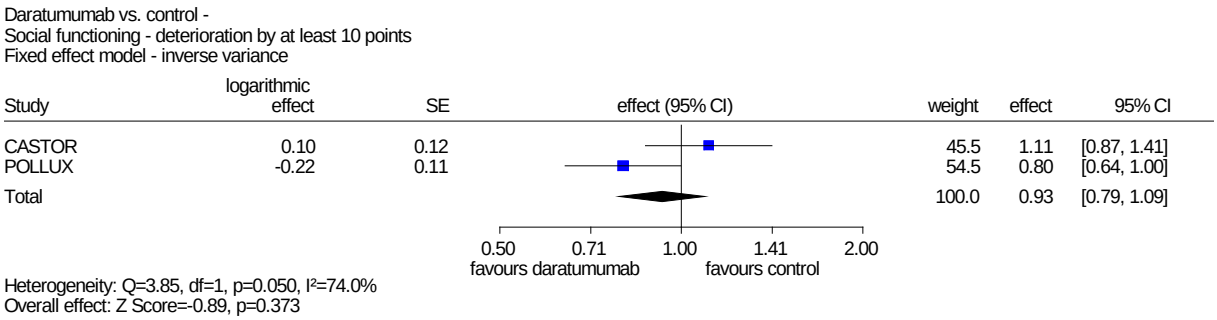

Figure 16: Meta-analysis, health-related quality of life: social functioning, deterioration by at least 10 points, daratumumab vs. control; effect estimate: HR

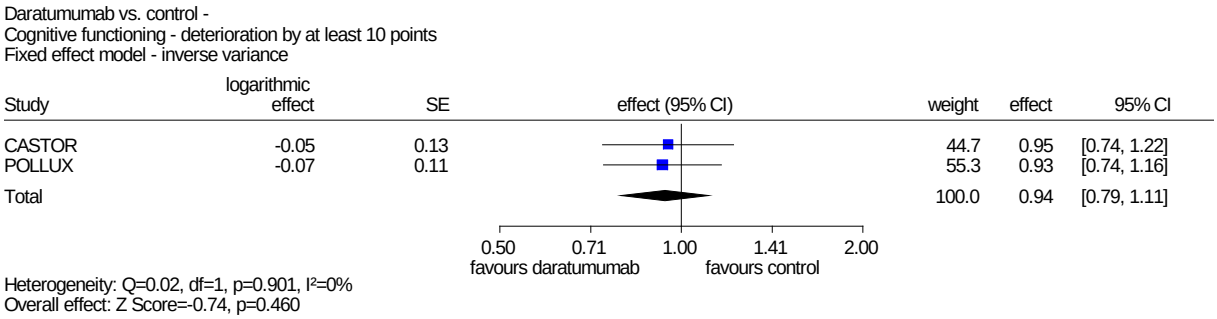

Figure 17: Meta-analysis, health-related quality of life: cognitive functioning, deterioration by at least 10 points, daratumumab vs. control; effect estimate: HR

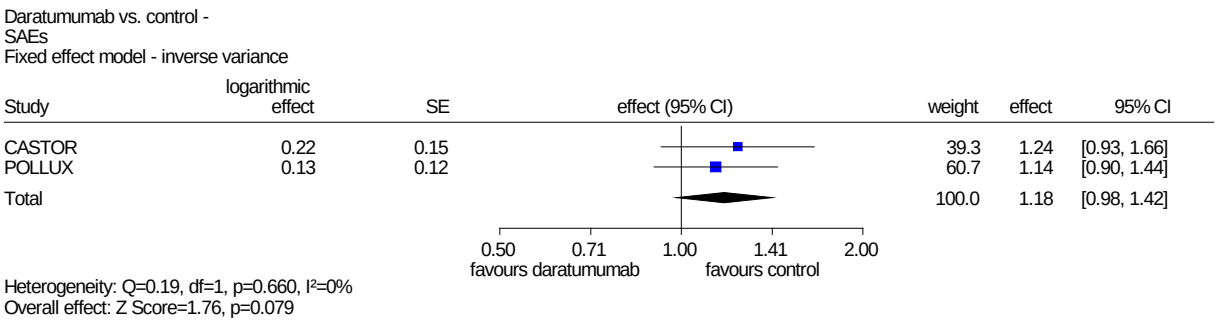

Figure 18: Meta-analysis, severe AEs, daratumumab vs. control; effect estimate: HR

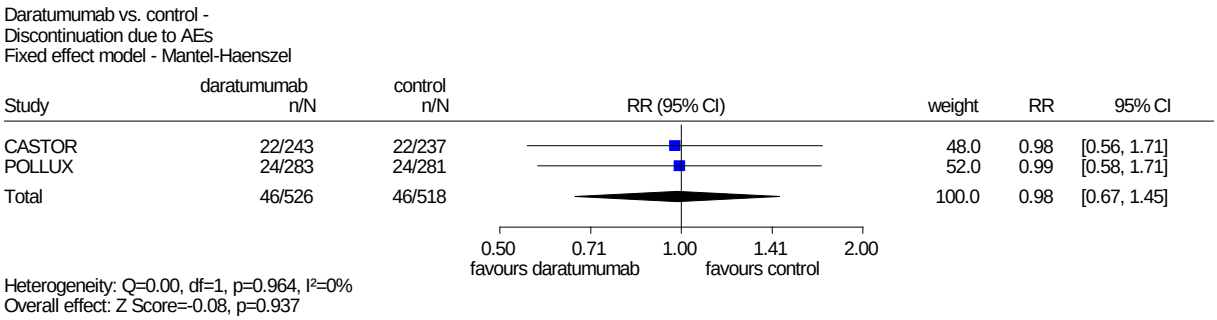

Figure 19: Meta-analysis, discontinuation due to AEs (of all drug components), daratumumab vs. control; effect estimate: RR

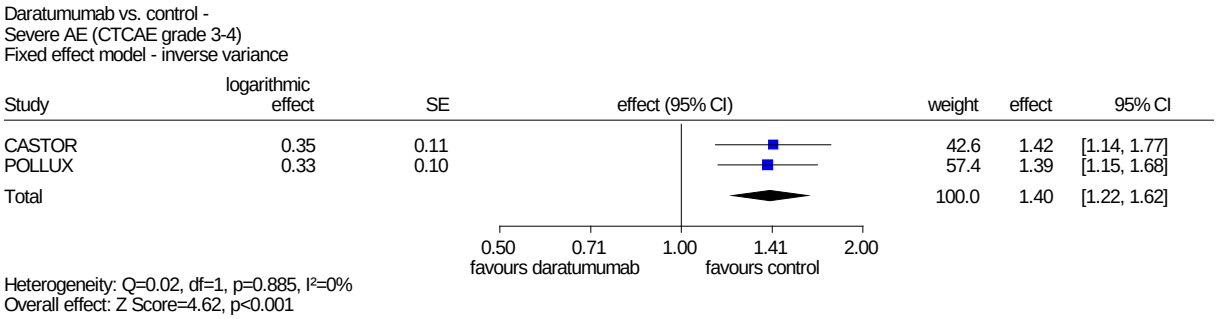

Figure 20: Meta-analysis, severe AEs (CTCAE grade 3–4), daratumumab vs. control; effect estimate: HR

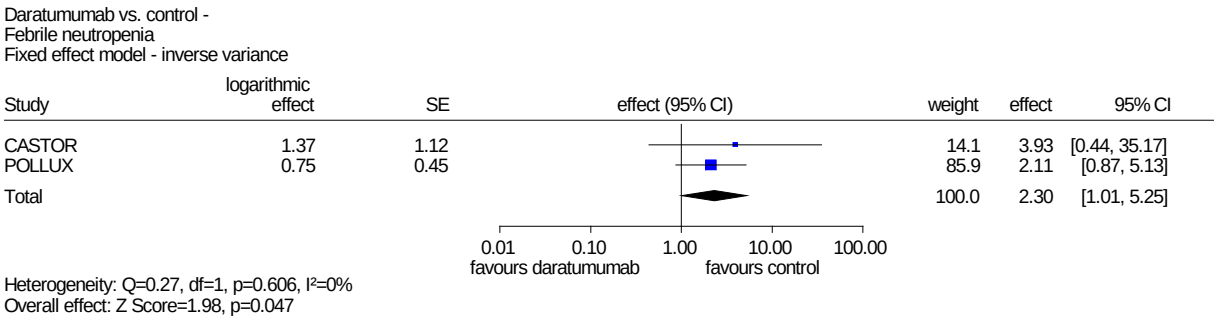

Figure 21: Meta-analysis, febrile neutropenia (PT), daratumumab vs. control; effect estimate: HR

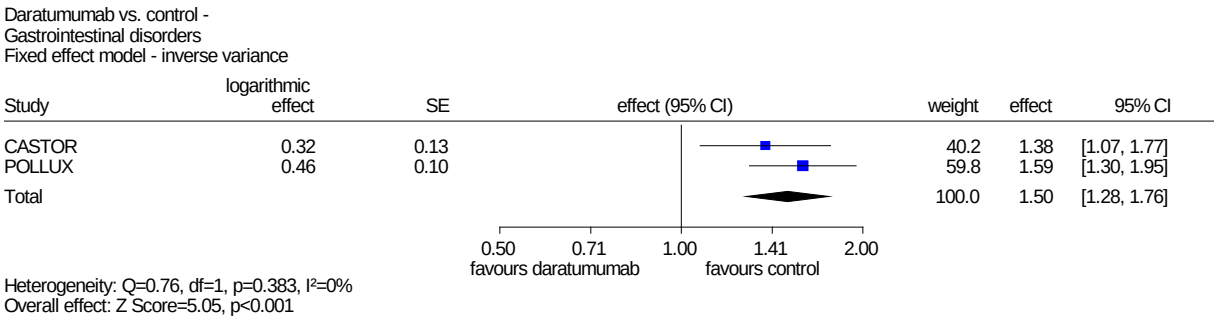

Figure 22: Meta-analysis, gastrointestinal disorders (SOC), daratumumab vs. control; effect estimate: HR

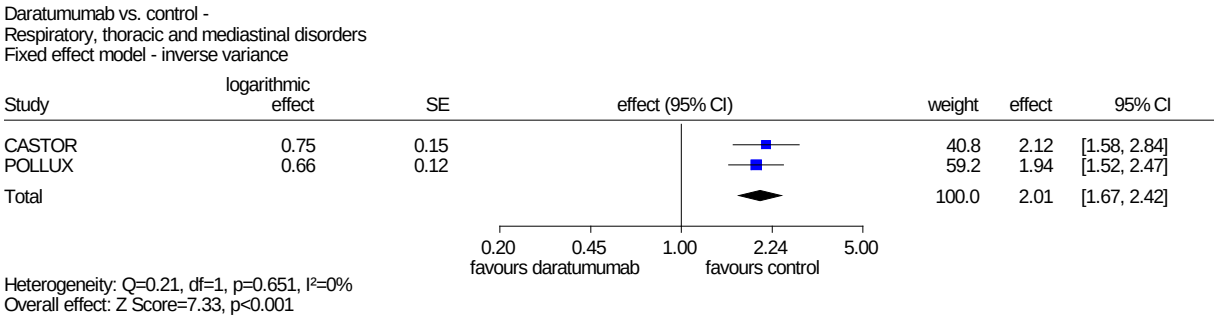

Figure 23: Respiratory, thoracic and mediastinal disorders (SOC), daratumumab vs. control; effect estimate: HR

Appendix B – Kaplan-Meier curves on results of the CASTOR study

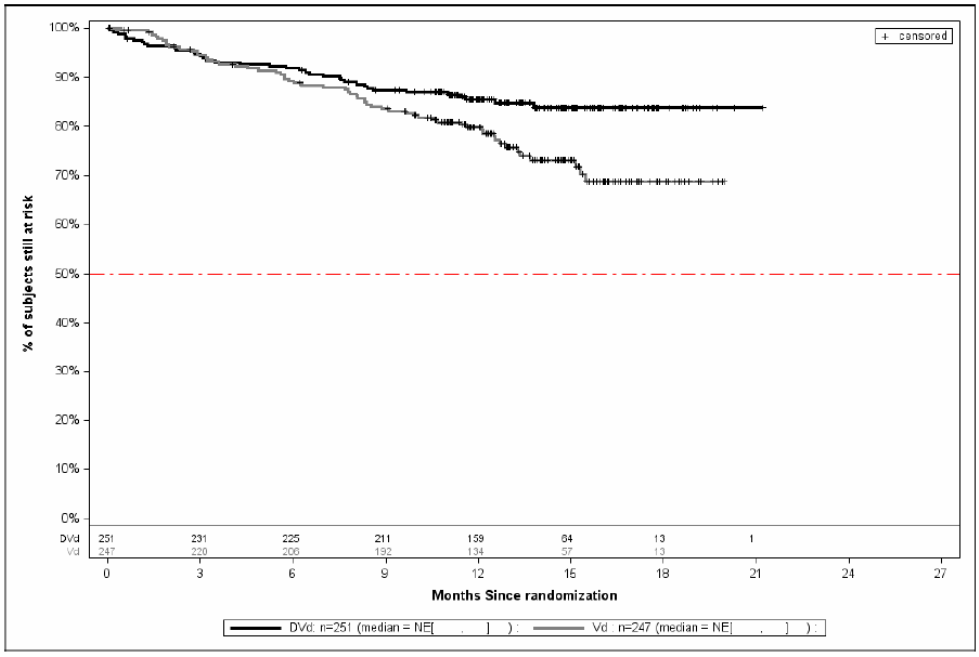

Figure 24: Kaplan-Meier on overall survival from the CASTOR study at the second data cut-off (30 June 2016)

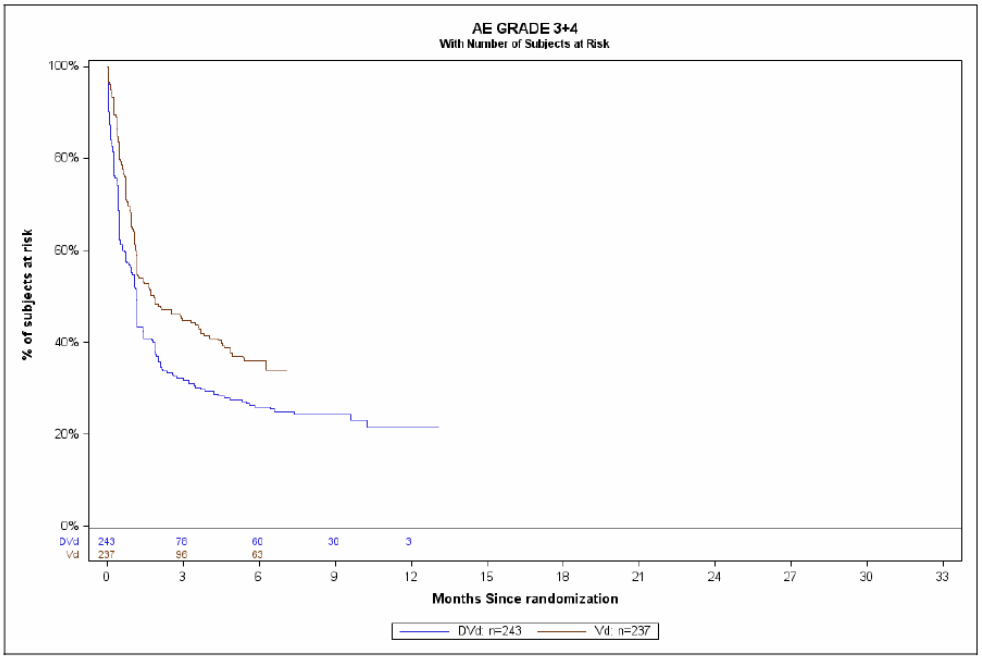

Figure 25: Kaplan-Meier curve for severe AEs (CTCAE grade 3–4) from the CASTOR study at the first data cut-off (11 January 2016)

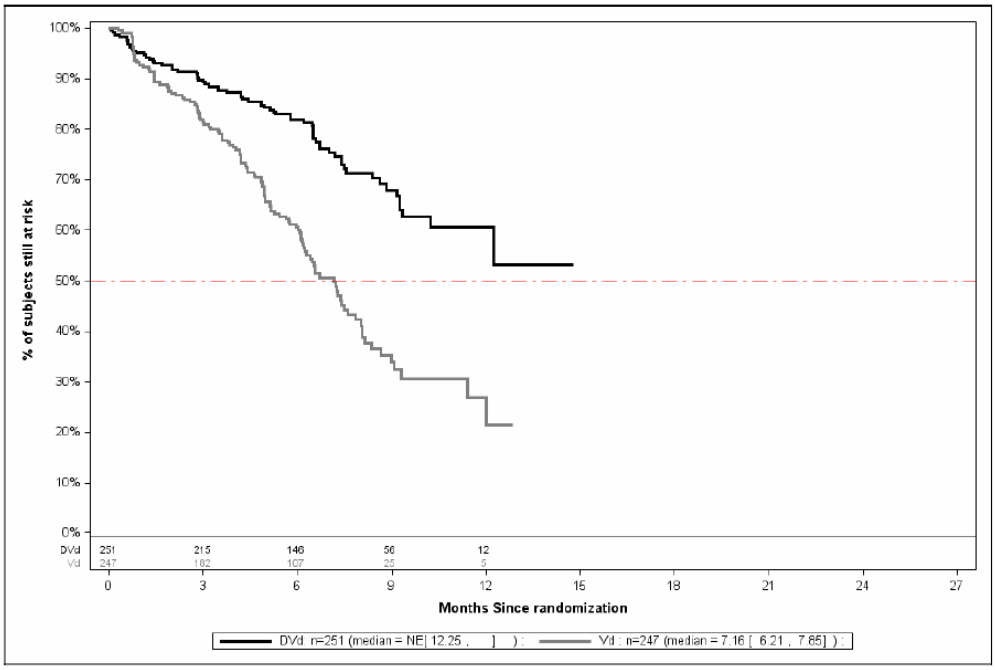

Figure 26: Kaplan-Meier curve on progression-free survival from the CASTOR study at the first data cut-off (11 January 2016)

Appendix C – Results on side effects in the CASTOR study

Table 12: Common AEs (in the SOC and in the PT ≥ 10% in at least one study arm) – RCT, direct comparison: daratumumab + bortezomib + dexamethasone vs. bortezomib + dexamethasone

Study	Patients with event n (%)	
SOC[a] PT[a]	**Daratumumab + bortezomib + dexamethasone N = 243**	**Bortezomib + dexamethasone N = 237**
CASTOR		
Overall rate of AEs (second data cut-off: 30 June 2016)	240 (98.8)	226 (95.4)
Infections and infestations	177 (72.8)	129 (54.4)
Upper respiratory tract infection	72 (29.6)	43 (18.1)
Bronchitis	32 (13.2)	15 (6.3)
Pneumonia	33 (13.6)	28 (11.8)
Gastrointestinal disorders	155 (63.8)	111 (46.8)
Diarrhoea	83 (34.2)	53 (22.4)
Constipation	52 (21.4)	38 (16.0)
Nausea	34 (14.0)	27 (11.4)
Vomiting	27 (11.1)	9 (3.8)
Blood and lymphatic system disorders	165 (67.9)	137 (57.8)
Neutropenia	45 (18.5)	23 (9.7)
Anaemia	67 (27.6)	75 (31.6)
Thrombocytopenia	145 (59.7)	105 (44.3)
Lymphopenia	32 (13.2)	9 (3.8)
General disorders and administration site conditions	134 (55.1)	125 (52.7)
Fatigue	53 (21.8)	58 (24.5)
Pyrexia	42 (17.3)	28 (11.8)
Oedema peripheral	44 (18.1)	20 (8.4)
Asthenia	24 (9.9)	37 (15.6)
Respiratory, thoracic and mediastinal disorders	137 (56.4)	78 (32.9)
Cough	66 (27.2)	30 (12.7)
Dyspnoea	45 (18.5)	21 (8.9)
Musculoskeletal and connective tissue disorders	124 (51.0)	88 (37.1)
Back pain	44 (18.1)	24 (10.1)
Arthralgia	29 (11.9)	13 (5.5)
Pain in extremity	26 (10.7)	16 (6.8)

(continued)

Table 12: Common AEs (in the SOC and in the PT ≥ 10% in at least one study arm) – RCT, direct comparison: daratumumab + bortezomib + dexamethasone vs. bortezomib + dexamethasone (continued)

Study	**Patients with event n (%)**	
SOC[a] PT[a]	**Daratumumab + bortezomib + dexamethasone N = 243**	**Bortezomib + dexamethasone N = 237**
Nervous system disorders	158 (65.0)	131 (55.3)
Headache	27 (11.1)	14 (5.9)
Peripheral sensory neuropathy	120 (49.4)	90 (38.0)
Dizziness	25 (10.3)	25 (10.5)
Neuralgia	33 (13.6)	26 (11.0)
Metabolism and nutrition disorders	99 (40.7)	66 (27.8)
Decreased appetite	26 (10.7)	12 (5.1)
Hypokalaemia	25 (10.3)	11 (4.6)
Skin and subcutaneous tissue disorders	60 (24.7)	32 (13.5)
Psychiatric disorders	71 (29.2)	54 (22.8)
Insomnia	42 (17.3)	36 (15.2)
Vascular disorders	57 (23.5)	33 (13.9)
Investigations	52 (21.4)	23 (9.7)

a: MedDRA version 18.0.

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 13: Common SAEs (in the SOC and in the PT ≥ 2% in at least one study arm) – RCT, direct comparison: daratumumab + bortezomib + dexamethasone vs. bortezomib + dexamethasone

Study	**Patients with event n (%)**	
SOC[a] PT[a]	**Daratumumab + bortezomib + dexamethasone N = 243**	**Bortezomib + dexamethasone N = 237**
CASTOR		
Overall rate of SAEs (second data cut-off: 30 June 2016)	118 (48.6)	81 (34.2)
Infections and infestations	59 (24.3)	44 (18.6)
Pneumonia	21 (8.6)	22 (9.3)
Bronchitis	7 (2.9)	2 (0.8)
Upper respiratory tract infection	6 (2.5)	2 (0.8)
Blood and lymphatic system disorders	15 (6.2)	2 (0.8)
Anaemia	8 (3.3)	1 (0.4)
Thrombocytopenia	6 (2.5)	1 (0.4)
Respiratory, thoracic and mediastinal disorders	17 (7.0)	7 (3.0)
General disorders and administration site conditions	10 (4.1)	12 (5.1)
Pyrexia	5 (2.1)	4 (1.7)
Gastrointestinal disorders	13 (5.3)	8 (3.4)
Cardiac disorders	14 (5.8)	5 (2.1)
Atrial fibrillation	6 (2.5)	0 (0)
Musculoskeletal and connective tissue disorders	10 (4.1)	8 (3.4)
Nervous system disorders	11 (4.5)	5 (2.1)
Injury, poisoning and procedural complications	8 (3.3)	5 (2.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9 (3.7)	1 (0.4)
Renal and urinary disorders	8 (3.3)	4 (1.7)
Metabolism and nutrition disorders	6 (2.5)	7 (3.0)

a: MedDRA version 18.0.

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 14: Common CTCAE grade 3 or 4 AEs (in the SOC and in the PT ≥ 3% in at least one study arm) – RCT, direct comparison: daratumumab + bortezomib + dexamethasone vs. bortezomib + dexamethasone

Study	**Patients with event n (%)**	
SOC[a] PT[a]	**Daratumumab + bortezomib + dexamethasone N = 243**	**Bortezomib + dexamethasone N = 237**
CASTOR		
Overall rate of common CTCAE grade 3 or 4 AEs (second data cut-off: 30 June 2016)	193 (79.4)	149 (62.9)
Blood and lymphatic system disorders	132 (54.3)	95 (40.1)
Neutropenia	32 (13.2)	11 (4.6)
Anaemia	36 (14.8)	38 (16.0)
Thrombocytopenia	110 (45.3)	78 (32.9)
Lymphopenia	24 (9.9)	6 (2.5)
Infections and infestations	63 (25.9)	45 (19.0)
Pneumonia	22 (9.1)	23 (9.7)
Metabolism and nutrition disorders	34 (14.0)	24 (10.1)
Hyperglycaemia	9 (3.7)	6 (2.5)
General disorders and administration site conditions	20 (8.2)	22 (9.3)
Fatigue	12 (4.9)	8 (3.4)
Gastrointestinal disorders	20 (8.2)	9 (3.8)
Diarrhoea	9 (3.7)	3 (1.3)
Respiratory, thoracic and mediastinal disorders	30 (12.3)	11 (4.6)
Dyspnoea	9 (3.7)	2 (0.8)
Nervous system disorders	28 (11.5)	25 (10.5)
Peripheral sensory neuropathy	11 (4.5)	16 (6.8)
Vascular disorders	22 (9.1)	11 (4.6)
Hypertension	16 (6.6)	2 (0.8)
Musculoskeletal and connective tissue disorders	21 (8.6)	13 (5.5)
Cardiac disorders	11 (4.5)	7 (3.0)
Psychiatric disorders	7 (2.9)	7 (3.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (3.3)	1 (0.4)
Renal and urinary disorders	8 (3.3)	5 (2.1)
Injury, poisoning and procedural complications	8 (3.3)	5 (2.1)

a: MedDRA version 18.0.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 15: Common AEs that led to treatment discontinuation (in the SOC and in the PT ≥ 1% in at least one study arm) – RCT, direct comparison: daratumumab + bortezomib + dexamethasone vs. bortezomib + dexamethasone

Study	**Patients with event n (%)**	
SOC[a] PT[a]	**Daratumumab + bortezomib + dexamethasone N = 243**	**Bortezomib + dexamethasone N = 237**
CASTOR		
Overall rate of common AEs that led to treatment discontinuation (second data cut-off: 30 June 2016)	22 (9.1)	22 (9.3)
Infections and infestations	7 (2.9)	5 (2.1)
Pneumonia	3 (1.2)	1 (0.4)
Nervous system disorders	3 (1.2)	10 (4.2)
Peripheral sensory neuropathy	1 (0.4)	6 (2.5)
Cardiac disorders	4 (1.6)	2 (0.8)
Respiratory, thoracic and mediastinal disorders	5 (2.1)	1 (0.4)

a: MedDRA version 18.0.

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