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Elotuzumab (multiple myeloma) –

Addendum to Commission A16-32[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BPI-SF	Brief Pain Inventory-Short Form
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EORTC QLQ-MY20	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Multiple Myeloma Module 20
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
MID	minimally important difference
MMRM	mixed-effects model repeated measures
PFS	progression-free survival
SAE	serious adverse event
SD	standard deviation
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 11 October 2016, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A16-32 (Elotuzumab – Benefit assessment according to §35a Social Code Book (SGB) V [1]).

The pharmaceutical company (hereinafter referred to as "the company") had presented the ELOQUENT-2 study [3-7] in its dossier on elotuzumab [2]. The study was assessed as not relevant in dossier assessment A16-32 because the dosing scheme in the control arm of the ELOQUENT-2 study deviated notably from the approval both in the dosage of dexamethasone in the first 4 treatment cycles (only one third of the recommended dose per cycle) and due to the generally missing pulse administration, and therefore did not represent the appropriate comparator therapy (ACT).

The G-BA commissioned IQWiG to assess the ELOQUENT-2 study and the results of the second data cut-off (29 October 2015) on the outcomes "adverse events (AEs)" subsequently submitted.

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

2 Assessment of the ELOQUENT-2 study

In accordance with the commission, the ELOQUENT-2 study is assessed in the following sections.

2.1 Study design and study characteristics

Tables presenting the study and intervention characteristics can be found in Appendix A of the dossier assessment on Commission A16-32.

The ELOQUENT-2 study was a multinational, randomized, open-label study. It included pretreated patients with refractory or relapsed multiple myeloma. The population included concurs with the approved therapeutic indication of elotuzumab.

Elotuzumab in combination with lenalidomide and low-dose dexamethasone was compared with lenalidomide in combination with low-dose dexamethasone in the ELOQUENT-2 study. A total of 646 patients were included (intervention arm: N = 321; control arm: N = 325). Except dexamethasone in the control arm, the interventions were used in compliance with the approval. In contrast to the approval of lenalidomide [8] (which also specifies the dosage of dexamethasone), dexamethasone in the control arm was used at a low dose and without pulse administration. A detailed description of this can be found in the dossier assessment on Commission A16-32.

Treatment in the ELOQUENT-2 study was conducted until disease progression or unacceptable toxicities. The final analysis was planned on the basis of the outcome "progression-free survival (PFS)"; it was planned after 466 events. A predefined interim analysis of the outcome "PFS" was conducted when 70% of the planned events had occurred and at least 2 years after the first patient had been enrolled in the study (data cut-off from 29 October 2014). The outcomes on morbidity, health-related quality of life and side effects were also analysed at this time point. A predefined interim analysis for the outcome "overall survival" was conducted at the data cut-off from 29 October 2015. According to Module 4 of the dossier, the final analysis for the outcome "overall survival" is expected for October 2018.

At the first data cut-off, 40.2% of the patients in the intervention arm and 52.3% of the patient in the control arm had received subsequent systemic treatments. At the second data cut-off, these were 48.0% and 58.2%. At the time point of the first data cut-off, the most common reason for such subsequent systemic treatment was disease progression (34.6% versus 42.5%); there was no information on this for the time point of the second data cut-off.

2.2 Presentation of the results

The mean treatment duration at the second data cut-off (29 October 2015) was 20.27 (standard deviation [SD]: 13.33) months (median: 17.28 months) in the intervention arm and 15.44 (SD: 11.81) months (median: 12.45 months) in the control arm. The mean observation period (presumably for the outcome "overall survival") was 28.56 (SD: 11.62)

months (median: 33.15 months) in the intervention arm and 26.29 (SD: 12.77) months (median: 31.84 months) in the control arm. Corresponding information for the first data cut-off was only available for individual drug components, but not for the combinations as a whole. Observation of the outcomes on morbidity ended with the end of treatment; for AE outcomes, the patients were followed-up until 60 days after the end of treatment.

Data cut-offs and data availability

Table 1 shows for which outcomes data from the individual data cut-off dates were available.

Table 1: Overview of the data from the ELOQUENT-2 study available for the assessment – RCT, direct comparison: elotuzumab + lenalidomide + low-dose dexamethasone vs. lenalidomide + low-dose dexamethasone

Study **Outcome category** **Outcome**	**Data cut-off 1 (29 Oct 2014)**	**Data cut-off 2 (29 Oct 2015 for OS and 10 Aug 2015[a] for side effects)**
ELOQUENT-2		
Mortality		
Overall survival	Yes	Yes
Morbidity		
Disease-related pain (BPI-SF)	Yes	No
Symptom scales (EORTC QLQ-C30 and EORTC QLQ-MY20)	Yes	No
Health-related quality of life		
Functional scales (EORTC QLQ-C30 and EORTC QLQ-MY20)	Yes	No
Side effects		
SAEs, severe AEs (CTCAE grade 3 and 4)	Yes	Yes
Discontinuation due to AEs	No[b]	No[b]

a: Discrepant information on the time point of the data cut-off for side effects between data subsequently submitted and Module 4.
b: No information on discontinuation of all treatment components.
AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-MY20: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Multiple Myeloma Module 20; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Except for the outcome “discontinuation due to AEs”, analyses at the first data cut-off were available for all patient-relevant outcomes. In addition, data from the second data cut-off were available for the outcomes of the categories “mortality” and “side effects” (except discontinuation due to AEs). Where possible, the second data cut-off was used for the present addendum.

The outcomes on morbidity and side effects were recorded until the end of the treatment (e.g. due to progression). About 60% of the patients in the intervention arm and about 71% of the patients in the control arm had progression until the first data cut-off. Only analyses on discontinuation of at least one drug component were available for the outcome "discontinuation due to AEs". Analyses on the discontinuation of all drug components of a treatment group were relevant for the assessment, however.

Characteristics of the study population

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

Table 2: Characteristics of the study population – RCT, direct comparison: elotuzumab + lenalidomide + low-dose dexamethasone vs. lenalidomide + low-dose dexamethasone

Study Characteristics Category	**E-Ld**	**Ld**
ELOQUENT-2	N[a] = 321	N[a] = 325
Age [years], mean (SD)	66.2 (9.3)	65.3 (10.3)
Sex [F/M], %	40/60	41/59
Ethnicity, n (%)		
White	264 (82.2)	280 (86.2)
Asian	33 (10.3)	31 (9.5)
Black/African American	13 (4.0)	10 (3.1)
Other/not reported	11 (3.4)[b]	4 (1.2)[b]
Type of myeloma, n (%)		
IgG	218 (67.9)	234 (72.0)
IgA	69 (21.5)	62 (19.1)
IgM	1 (0.3)	1 (0.3)
IgD	3 (0.9)	5 (1.5)
Light chain disease	27 (8.4)	20 (6.2)
Biclonal myeloma	2 (0.6)	3 (0.9)
Not classified	1 (0.3)	0 (0)
ISS stage, n (%)		
I	141 (43.9)	138 (42.5)
II	102 (31.8)	105 (32.3)
III	66 (20.6)	68 (20.9)
Not reported	12 (3.7)	14 (4.3)
Disease duration: time between first diagnosis and randomization [months], mean (SD)	52.1 (38.1)	50.6 (36.3)
ECOG PS, n (%)		
0	159 (49.5)	145 (44.6)
1	138 (43.0)	146 (44.9)
2	24 (7.5)	34 (10.5)
Number of prior therapies, n (%)		
1	151 (47.0)	159 (48.9)
≥ 2	170 (53.0)	166 (51.1)
Prior IMiD therapies, n (%)		
None	155 (48.3)	151 (46.5)
Thalidomide only	150 (46.7)	153 (47.1)
Other	16 (5.0)	21 (6.5)

(continued)

Table 2: Characteristics of the study population – RCT, direct comparison: elotuzumab + lenalidomide + low-dose dexamethasone vs. lenalidomide + low-dose dexamethasone (continued)

Study Characteristics Category	**E-Ld**	**Ld**
ELOQUENT-2	N[a] = 321	N[a] = 325
Prior non-drug therapies, n (%)		
Stem cell transplantation	167 (52.0)	185 (56.9)
Radiotherapy	90 (28.0)	61 (18.8)
Surgical intervention	36 (11.2)	35 (10.8)
Treatment discontinuation[c] first data cut-off, n (%)	206 (64.6)	250 (79.1)
Treatment discontinuation[c] second data cut-off, n (%)	236 (74.0)	273 (86.4)
Study discontinuation, n (%)	ND	ND

a: Number of randomized patients.
b: Institute's calculation.
c: Discontinuation of all treatment components.
ECOG PS: Eastern Cooperative Oncology Group Performance Status; E-Ld: elotuzumab + lenalidomide + low-dose dexamethasone; F: female; Ig: immunoglobulin; IMiD: immunomodulatory drugs; ISS: International Staging System; Ld: lenalidomide + low-dose dexamethasone; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The patient characteristics were comparable between the treatment groups. The majority of the patients included were allocated to the International Staging System (ISS) stage I and II and had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1. About half of the patients were pretreated with 2 or more therapies. At both data cut-offs, somewhat more patients had discontinued treatment of all combination partners in the control arm than in the intervention arm with a similar difference between the treatment arms at the first data cut-off and at the second data cut-off.

Table 3 shows the risk of bias at study level.

Table 3: Risk of bias at study level – RCT, direct comparison: elotuzumab + lenalidomide + low-dose dexamethasone vs. lenalidomide + low-dose 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			
ELOQUENT-2	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level was rated as low.

Results

Table 4 shows the risk of bias for the patient-relevant outcomes.

Table 4: Risk of bias at study and outcome level – RCT, direct comparison: elotuzumab + lenalidomide + low-dose dexamethasone vs. lenalidomide + low-dose dexamethasone

Study	Study level	Outcomes								
		Overall survival	Disease-related pain (BPI-SF)	Symptoms (EORTC QLQ-C30 symptom scales)	Symptoms (EORTC QLQ-MY20 symptom scales)	Health-related quality of life (EORTC QLQ-C30 functional scales)	Health-related quality of life (EORTC QLQ-MY20 functional scales)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade 3 or 4)
ELOQUENT-2	L	L	H[a, b]	H[a, c]	H[a, c]	H[a, c]	H[a, c]	H[c]	H[a, c]	H[c]
a: Lack of blinding in subjective recording of outcomes. b: Relevantly high proportion of patients not included in the analysis (> 10%). c: Different observation periods with potentially informative censoring. AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-MY20: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Multiple Myeloma Module 20; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus										

Except for overall survival, there was a high risk of bias for all outcomes. For the outcome "disease-related pain", this was due to the lack of blinding and a relevantly high proportion of patients not included in the analysis. For all other outcomes with high risk of bias, different observation periods with potentially informative censoring and, except for serious adverse events (SAEs) and severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade 3 or 4), the lack of blinding led to a high risk of bias.

Table 5 and Table 6 summarize the results on the comparison of the combination of elotuzumab, lenalidomide and low-dose dexamethasone versus the combination of lenalidomide and low-dose dexamethasone. Where necessary, the data presented by the company were supplemented with the Institute's calculations. For the data cut-offs considered in the present addendum, a Kaplan-Meier curve was only available for the outcome "overall survival" (see Appendix B).

Table 5: Results – RCT, direct comparison: elotuzumab + lenalidomide + low-dose dexamethasone vs. lenalidomide + low-dose dexamethasone

Study Outcome category Outcome	E-Ld N	E-Ld Median survival time in months [95% CI] Patients with event n (%)	Ld N	Ld Median survival time in months [95% CI] Patients with event n (%)	E-Ld vs. Ld HR [95% CI][a]; p-value[b]
ELOQUENT-2					
Mortality (second data cut-off: 29 October 2015)					
Overall survival	321	43.7 [40.3; NA] 136 (42.4)	325	39.6 [33.3; NA] 159 (48.9)	0.77 [0.61; 0.97]; 0.026
Morbidity (first data cut-off: 29 October 2014)					
Symptoms (EORTC QLQ-C30, deterioration by 10 points)					
Fatigue	321	1.9 [1.6; 2.3] 220 (68.5)	325	1.8 [1.5; 2.3] 219 (67.4)	0.89 [0.74; 1.08]; 0.238
Nausea/vomiting	321	6.0 [5.1; 7.8] 178 (55.5)	325	6.0 [4.0; 7.9] 173 (53.2)	0.95 [0.77; 1.17]; 0.630
Pain	321	3.31 [2.4; 4.2] 215 (67.0)	325	2.0 [1.5; 3.0] 201 (61.8)	0.85 [0.70; 1.03]; 0.090
Dyspnoea	321	4.2 [3.3; 6.0] 195 (60.7)	325	3.4 [2.4; 4.2] 186 (57.2)	0.88 [0.72; 1.07]; 0.203
Insomnia	321	2.8 [2.0; 4.2] 205 (63.9)	325	3.7 [2.6; 5.3] 186 (57.2)	1.04 [0.85; 1.27]; 0.719
Appetite loss	321	3.3 [2.5; 4.7] 205 (63.9)	325	4.1 [3.3; 5.8] 187 (57.5)	1.09 [0.89; 1.33]; 0.415
Constipation	321	2.4 [2.1; 3.4] 197 (61.4)	325	2.4 [2.0; 3.3] 190 (58.5)	0.98 [0.80; 1.19]; 0.816
Diarrhoea	321	5.0 [4.1; 5.6] 200 (62.3)	325	4.2 [3.5; 5.1] 189 (58.2)	0.98 [0.81; 1.20]; 0.874
Symptoms (EORTC QLQ-MY20, deterioration by 10 points)					
Disease-related symptoms	321	2.3 [1.6; 3.0] 209 (65.1)	325	1.8 [1.5; 2.8] 206 (63.4)	0.92 [0.76; 1.12]; 0.401
Side effects of treatment	321	1.5 [1.4; 1.6] 233 (72.6)	325	1.4 [1.4; 1.5] 234 (72.0)	0.99 [0.82; 1.19]; 0.893

(continued)

Table 5: Results – RCT, direct comparison: elotuzumab + lenalidomide + low-dose dexamethasone vs. lenalidomide + low-dose dexamethasone (continued)

Study Outcome category Outcome	E-Ld N	E-Ld Median survival time in months [95% CI] Patients with event n (%)	Ld N	Ld Median survival time in months [95% CI] Patients with event n (%)	E-Ld vs. Ld HR [95% CI][a]; p-value[b]
ELOQUENT-2					
Health-related quality of life (first data cut-off: 29 October 2014)					
EORTC QLQ-C30 functional scales (deterioration by 10 points)					
General health status	321	1.5 [1.4; 1.9] 226 (70.4)	325	1.5 [1.4; 1.9] 229 (70.5)	0.91 [0.76; 1.10]; 0.325
Physical functioning	321	1.5 [1.4; 1.8] 232 (72.3)	325	1.7 [1.4; 2.3] 210 (64.6)	1.08 [0.90; 1.30]; 0.424
Role functioning	321	2.3 [1.7; 3.3] 216 (67.3)	325	2.0 [1.6; 2.4] 202 (62.2)	0.95 [0.78; 1.15]; 0.599
Emotional functioning	321	1.8 [1.5; 2.3] 223 (69.5)	325	2.1 [1.6; 2.5] 201 (61.8)	1.03 [0.85; 1.25]; 0.751
Social functioning	321	2.5 [1.8; 3.2] 206 (64.2)	325	2.3 [1.7; 2.6] 212 (65.2)	0.89 [0.74; 1.08]; 0.248
Cognitive functioning	321	2.3 [1.7; 3.2] 210 (65.4)	325	3.2 [2.4; 3.5] 204 (62.8)	1.04 [0.86; 1.26]; 0.676
EORTC QLQ-MY20 (deterioration by 10 points)					
Future perspective	321	3.3 [2.3; 5.4] 185 (57.6)	325	4.7 [3.3; 7.3] 169 (52.0)	1.10 [0.90; 1.36]; 0.361
Body image	321	5.4 [4.2; 6.7] 175 (54.5)	325	4.2 [3.2; 5.4] 175 (53.8)	0.87 [0.71; 1.08]; 0.205
Side effects (second data cut-off: 10 August 2015[c])					
AEs (supplementary information)	318	0.1 [0.1; 0.1] 316 (99.4)	317	0.2 [0.1; 0.2] 314 (99.1)	–
SAEs	318	11.0 [9.0; 13.0] 223 (70.1)	317	13.4 [10.2; 18.6] 190 (59.9)	1.06 [0.87; 1.29]; 0.572
Severe AEs (CTCAE grade 3 or 4)	318	2.4 [1.6; 3.3] 282 (88.7)	317	3.1 [1.9; 4.2] 248 (78.2)	1.22 [1.02; 1.45]; 0.026
Discontinuation due to AEs[d]	318	ND	317	ND	ND

(continued)

Table 5: Results – RCT, direct comparison: elotuzumab + lenalidomide + low-dose dexamethasone vs. lenalidomide + low-dose dexamethasone (continued)

a: For mortality and side effects: Cox proportional hazards model adjusted regarding ß2-microglobulin, number of prior therapies and IMiD pretreatment according to the IVRS. For morbidity and health-related quality of life: Cox proportional hazards model adjusted regarding baseline value.
b: Stratified log-rank test.
c: Discrepant information on the time point of the data cut-off for side effects between data subsequently submitted and Module 4.
d: No information available on the discontinuation of all treatment components. 96 (30.2%) patients in the E-Ld arm and 94 (29.7%) patients in the Ld arm discontinued at least one treatment component. Median time (months) until discontinuation of at least one treatment component [95% CI]: NA [38.0; NA] for E-Ld arm and NA [30.8; NA] for Ld arm; HR: 0.81 [0.61; 1.08]; 0.158.

AE: adverse events; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; E-Ld: elotuzumab + lenalidomide + low-dose dexamethasone; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer-Core 30; EORTC QLQ-MY20: European Organisation for Research and Treatment of Cancer-Multiple Myeloma Module 20; IMiD: immunomodulatory drugs; IVRS: interactive voice response system; HR: hazard ratio; Ld: lenalidomide + low-dose dexamethasone; 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; vs.: versus

Table 6: Results (morbidity) – RCT, direct comparison: elotuzumab + lenalidomide + low-dose dexamethasone vs. lenalidomide + low-dose dexamethasone

Study Outcome category Outcome	E-Ld			Ld			E-Ld vs. Ld
	N[a]	Values at start of study mean (SD)	Change at end of study mean[b] (SE)	N[a]	Values at start of study mean (SD)	Change at end of study mean[b] (SE)	MD [95% CI][b]; p-value
ELOQUENT-2							
Morbidity (first data cut-off: 29 October 2014)							
Disease-related pain (BPI-SF)[c]							
Overall pain intensity	289	2.6 (2.1)	−0.0 (0.1)	290	2.9 (2.5)	0 (0.1)	−0.02 [−0.25; 0.21]; 0.875
Worst pain	289	3.6 (2.8)	−0.1 (0.1)	290	3.8 (3.0)	−0.1 (0.1)	−0.03 [−0.32; 0.26]; 0.823
Least pain	289	1.8 (2.0)	0.1 (0.1)	290	2.1 (2.3)	0.2 (0.1)	−0.02 [−0.25; 0.20]; 0.833
Average pain	289	2.8 (2.2)	−0.1 (0.1)	290	3.2 (2.6)	−0.2 (0.1)	0.03 [−0.22; 0.28]; 0.803
Pain now	289	2.1 (2.3)	0 (0.1)	290	2.6 (2.7)	0.1 (0.1)	−0.06 [−0.31; 0.19]; 0.622
Overall pain interference	289	2.5 (2.4)	0.4 (0.1)	290	2.8 (2.7)	0.3 (0.1)	0.03 [−0.24; 0.29]; 0.845
With general activity	289	2.8 (2.9)	0.3 (0.1)	290	3.2 (3.2)	0.3 (0.1)	0 [−0.29; 0.30]; 0.984
With mood	289	2.4 (2.6)	0.3 (0.1)	290	2.7 (2.9)	0.3 (0.1)	−0.04 [−0.34; 0.25]; 0.773
With walking ability	289	2.8 (3.1)	0.2 (0.1)	290	3.2 (3.2)	0.2 (0.2)	−0.03 [−0.35; 0.29]; 0.875
With normal work/endurance	289	3.0 (3.2)	0.3 (0.1)	290	3.3 (3.3)	0.3 (0.2)	−0.07 [−0.39; 0.25]; 0.653
With relations with other people	289	1.7 (2.4)	0.6 (0.1)	290	2.0 (2.6)	0.7 (0.1)	−0.04 [−0.33; 0.26]; 0.802
With sleep	289	2.1 (2.6)	0.3 (0.1)	290	2.4 (2.9)	0.2 (0.1)	0.11 [−0.19; 0.40]; 0.472
With enjoyment of life	289	2.5 (2.9)	0.3 (0.1)	290	3.0 (3.2)	0.2 (0.1)	0.06 [−0.25; 0.37]; 0.724

(continued)

Table 6: Results (morbidity) – RCT, direct comparison: elotuzumab + lenalidomide + low-dose dexamethasone vs. lenalidomide + low-dose dexamethasone (continued)

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: MMRM with treatment, documentation time and value at the start of the study as fixed effects.
c: A negative change compared with the start of the study indicates improvement; a negative effect estimate therefore indicates an advantage of elotuzumab.
BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; E-Ld: elotuzumab + lenalidomide + low-dose dexamethasone; Ld: lenalidomide + low-dose dexamethasone; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; vs.: versus

Mortality

Overall survival

A statistically significant difference in favour of the intervention arm versus the control arm was shown for the outcome "overall survival". There were effect modifications by disease severity: Proof of an effect modification was shown for ECOG PS and an indication of an effect modification in each case was shown for the characteristics "myeloma risk" and "number of prior therapies". The results on the subgroups for the outcome "overall survival" consistently showed that there were effects of elotuzumab only in patients with a higher severity grade of the disease (see below for a detailed description).

Overall, an advantage of elotuzumab in combination with lenalidomide and low-dose dexamethasone in comparison with lenalidomide in combination with low-dose dexamethasone was shown for patients with an ECOG PS of 2. There was no advantage for patients with an ECOG PS of 0 to 1.

Morbidity

Symptoms

The outcome "symptoms" was recorded with the symptom scales of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and of the EORTC QLQ-Multiple Myeloma Module (MY) 20. The company presented both analyses for the time to deterioration by 10 points and analyses on the mean change of the outcome under treatment (using the mixed-effects model repeated measures [MMRM]). The responder analyses with the validated minimally important difference (MID) of 10 points were regarded to be the more adequate analyses and therefore used.

Overall, there were no statistically significant differences between the treatment groups for symptoms.

Disease-related pain

The outcome "pain" was recorded with the Brief Pain Inventory-Short Form (BPI-SF). The company presented both an analysis for the time to deterioration for the question of the worst pain with deterioration by 3 points and analyses on the mean change of the outcome under treatment (using the MMRM). Since the company provided no sufficient justification for the threshold value of 3 points, only the MMRM analyses were considered.

There were no statistically significant differences between the treatment groups for the outcome "pain".

Health-related quality of life

The outcome "health-related quality of life" was recorded with the functional scales of the EORTC QLQ-C30 and EORTC QLQ-MY20. The company presented both analyses for the time to deterioration (by 10 points) and analyses on the change in comparison with the baseline value (using the MMRM). The responder analyses with the validated MID of 10 were regarded as the more adequate analyses and therefore used.

Overall, there were no statistically significant differences between the treatment groups for health-related quality of life.

Side effects

Serious adverse events

There was no statistically significant difference between the treatment groups for the outcome "SAEs".

Severe adverse events (CTCAE grade 3 or 4)

For the outcome "severe AEs", the company presented no analyses for CTCAE grades ≥ 3, but only for the CTCAE grades 3 or 4. The analysis was conducted with the most severe grade a patient had. This means that patients who had a grade 3 or 4 event, but also a grade 5 event, were not considered in the analysis of the severe AEs (CTCAE grade 3 or 4) presented by the company. For the second data cut-off, this concerned 11.9% in the intervention arm and 13.2% in the control arm.

A statistically significant effect to the disadvantage of the intervention arm versus the control arm was shown for the outcome "severe AEs" (CTCAE grade 3 or 4).

Discontinuation due to adverse events

Analyses on the discontinuation of all drug components were relevant for the outcome "discontinuation due to AEs". These were not available for any of the 2 data cut-offs. Hence it was not possible to draw a conclusion on the advantage or disadvantage of elotuzumab combined with lenalidomide and low-dose dexamethasone.

Subgroups and other effect modifiers

Subgroup analyses on age (< 65 versus ≥ 65 years), sex and severity grade planned a priori were considered in the present assessment.

For the outcome "overall survival", results are presented if there was at least an indication of an interaction between treatment effect and subgroup characteristic. For all other outcomes, only results for which there was proof of an interaction are presented due to the different treatment durations and resulting different observation periods and the potentially informative censoring. The prerequisite for proof of an effect modification is a statistically significant interaction with a p-value < 0.05. A p-value ≥ 0.05 and < 0.2 provides an indication of an effect modification. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

Table 7 summarizes the subgroup results on the comparison of the combination of elotuzumab, lenalidomide and low-dose dexamethasone versus the combination of lenalidomide and low-dose dexamethasone in the ELOQUENT-2 study.

Table 7: Subgroups (mortality) – RCT, direct comparison: elotuzumab + lenalidomide + low-dose dexamethasone vs. lenalidomide + low-dose dexamethasone

Study **Outcome category** **Outcome** **Characteristic** **Subgroup**	**E-Ld** **N**	**Median survival time in months [95% CI]** **Patients with event n (%)**	**Ld** **N**	**Median survival time in months [95% CI]** **Patients with event n (%)**	**E-Ld vs. Ld** **HR [95% CI][a]**	**p-value[b]**
ELOQUENT-2						
Mortality (second data cut-off: 29 October 2015)						
Overall survival						
ECOG PS						
0-1	297	NA [40.9; NA] 121 (40.7)	291	40.9 [36.9; NA] 130 (44.7)	0.86 [0.67; 1.10]	0.229
2	24	28.1 [16.5; NA] 15 (62.5)	34	12.9 [10.4; 16.8] 29 (85.3)	0.43 [0.23; 0.81]	0.007
Total					Interaction:	0.021[c]
Myeloma risk[d]						
High risk	60	29.8 [22.2; NA] 28 (46.7)	66	24.8 [11.7; 31.2] 43 (65.2)	0.60 [0.37; 0.97]	0.033
Low risk	14	NA [33.1; NA] 5 (35.7)	22	40.8 [35.2; NA] 9 (40.9)	0.84 [0.28; 2.52]	0.761
Normal risk	231	43.7 [40.1; NA] 100 (43.3)	221	47.6 [36.9; NA] 94 (42.5)	0.95 [0.72; 1.26]	0.732
Total					Interaction:	0.193[c]
Number of prior therapies						
1	151	42.9 [35.8; NA] 65 (43.0)	159	40.9 [35.0; NA] 73 (45.9)	0.92 [0.66; 1.29]	0.637
2 or 3	170	NA [40.1; NA] 71 (41.8)	166	33.6 [28.0; 41.3] 86 (51.8)	0.67 [0.49; 0.92]	0.013
Total					Interaction:	0.167[c]

a: Unstratified Cox model.
b: Unstratified log-rank test.
c: Unstratified Cox model with treatment, subgroup characteristic and the interaction term treatment*subgroup characteristic.
d: 16 (5%) patients in each arm were not considered in the analysis.
CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status;
E-Ld: elotuzumab + lenalidomide + low-dose dexamethasone; HR: hazard ratio; Ld: lenalidomide + low-dose dexamethasone; N: number of analysed patients; n: patients with event; NA: not achieved; RCT: randomized controlled trial; vs.: versus

Mortality

There were different effect modifications for the outcome "overall survival". Proof of an effect modification was shown for ECOG PS and an indication of an effect modification in

each case was shown for the characteristics “myeloma risk” and “number of prior therapies”. Overall, the available data can be summarized as effect modification by the severity grade of the disease.

A statistically significant difference in favour of the intervention arm versus the control arm was shown for patients with an ECOG PS of 2. No statistically significant difference between the treatment groups was shown for patients with an ECOG PS of 0 or 1. A statistically significant difference in favour of the intervention arm versus the control arm was shown for patients with high myeloma risk. No statistically significant difference between the treatment groups was shown for each of both subgroups with low and normal risk. A statistically significant difference in favour of the intervention arm versus the control arm was shown for patients with 2 or 3 prior therapies. No statistically significant difference between the treatment groups was shown for patients with one prior therapy.

Overall, the results of the subgroup analyses on severity grade for the outcome “overall survival” consistently showed that there were effects of elotuzumab only in patients with a higher severity grade of the disease. Since there was proof of an interaction for the ECOG PS, the subgroup analysis on the ECOG PS was used to interpret the results of the effect modification by severity grade. An advantage of elotuzumab in combination with lenalidomide and low-dose dexamethasone in comparison with lenalidomide in combination with low-dose dexamethasone was derived for patients with an ECOG PS of 2. There was no such advantage for patients with an ECOG PS of 0 and 1.

2.3 Summary

Table 8 shows the positive and negative effects resulting from the ELOQUENT-2 study for elotuzumab in combination with lenalidomide and low-dose dexamethasone in comparison with lenalidomide in combination with low-dose dexamethasone.

Table 8: Positive and negative effects for elotuzumab in combination with lenalidomide and low-dose dexamethasone vs. lenalidomide + low-dose dexamethasone

Positive effects	**Negative effects**
Mortality ▪ Overall survival ▫ Patients with ECOG PS 2	Severe/serious side effects ▪ Severe AEs (CTCAE grade 3 or 4)
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; ECOG PS: Eastern Cooperative Oncology Group Performance Status; vs.: versus	

In the overall consideration, there is a positive effect for the outcome “overall survival” in patients with an ECOG PS of 2. This is accompanied by a negative effect in severe AEs in the total population. It is to be noted for both effects that the dosage of dexamethasone administered in the control arm was notably below the approval-compliant dosage and therefore did not represent the ACT.

3 References

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Appendix A – Results on side effects

Table 9: Common AEs (in the SOC or in the PT ≥ 10% in at least one study arm) – RCT, direct comparison: elotuzumab + lenalidomide + low-dose dexamethasone vs. lenalidomide + low-dose dexamethasone

Study	Patients with event[b] n (%)	
SOC[a] PT[a]	E-Ld N = 318	Ld N = 317
ELOQUENT-2		
Overall rate of adverse events	316 (99.4)	314 (99.1)
General disorders and administration site conditions	272 (85.5)	238 (75.1)
Fatigue	154 (48.4)	128 (40.4)
Fever	122 (38.4)	79 (24.9)
Oedema peripheral	87 (27.4)	74 (23.3)
Asthenia	75 (23.6)	53 (16.7)
Infections and infestations	265 (83.3)	237 (74.8)
Nasopharyngitis	78 (24.5)	61 (19.2)
Upper respiratory tract infection	77 (24.2)	58 (18.3)
Bronchitis	62 (19.5)	54 (17.0)
Pneumonia	54 (17.0)	40 (12.6)
Respiratory tract infection	36 (11.3)	30 (9.5)
Lower respiratory tract infection	32 (10.1)	18 (5.7)
Gastrointestinal disorders	256 (80.5)	214 (67.5)
Diarrhoea	152 (47.8)	118 (37.2)
Constipation	114 (35.8)	88 (27.8)
Nausea	78 (24.5)	70 (22.1)
Vomiting	52 (16.4)	29 (9.1)
Abdominal pain	44 (13.8)	29 (9.1)
Dyspepsia	33 (10.4)	19 (6.0)
Musculoskeletal and connective tissue disorders	223 (70.1)	217 (68.5)
Muscle spasms	96 (30.2)	84 (26.5)
Back pain	95 (29.9)	91 (28.7)
Arthralgia	63 (19.8)	46 (14.5)
Pain in extremity	56 (17.6)	32 (10.1)
Musculoskeletal pain	45 (14.2)	30 (9.5)
Muscular weakness	37 (11.6)	26 (8.2)
Musculoskeletal chest pain	36 (11.3)	30 (9.5)
Bone pain	32 (10.1)	41 (12.9)

(continued)

Table 9: Common AEs (in the SOC or in the PT ≥ 10% in at least one study arm) – RCT, direct comparison: elotuzumab + lenalidomide + low-dose dexamethasone vs. lenalidomide + low-dose dexamethasone (continued)

Study	**Patients with event[b] n (%)**	
SOC[a] **PT[a]**	**E-Ld** **N = 318**	**Ld** **N = 317**
ELOQUENT-2		
Nervous system disorders	206 (64.8)	174 (54.9)
Headache	51 (16.0)	26 (8.2)
Peripheral neuropathy	48 (15.1)	27 (8.5)
Dizziness	46 (14.5)	37 (11.7)
Paresthesia	33 (10.4)	29 (9.1)
Dysgeusia	32 (10.1)	20 (6.3)
Peripheral sensory neuropathy	31 (9.7)	37 (11.7)
Blood and lymphatic system disorders	204 (64.2)	195 (61.5)
Anaemia	130 (40.9)	118 (37.2)
Neutropenia	108 (34.0)	137 (43.2)
Thrombocytopenia	88 (27.7)	72 (22.7)
Lymphopenia	42 (13.2)	24 (7.6)
Respiratory, thoracic and mediastinal disorders	201 (63.2)	169 (53.3)
Cough	105 (33.0)	60 (18.9)
Dyspnoea	71 (22.3)	60 (18.9)
Oropharyngeal pain	32 (10.1)	14 (4.4)
Skin and subcutaneous tissue disorders	189 (59.4)	147 (46.4)
Rash	61 (19.2)	58 (18.3)
Hyperhidrosis	38 (11.9)	23 (7.3)
Pruritus	33 (10.4)	28 (8.8)
Metabolism and nutrition disorders	183 (57.5)	155 (48.9)
Decreased appetite	67 (21.1)	41 (12.9)
Hyperglycaemia	58 (18.2)	43 (13.6)
Hypokalaemia	55 (17.3)	48 (15.1)
Hypocalcaemia	45 (14.2)	31 (9.8)
Investigations	157 (49.4)	128 (40.4)
Decreased weight	45 (14.2)	20 (6.3)
Blood creatinine increased	33 (10.4)	23 (7.3)
Alanine aminotransferase increased	25 (7.9)	33 (10.4)
Psychiatric disorders	140 (44.0)	122 (38.5)
Insomnia	76 (23.9)	84 (26.5)
Vascular disorders	126 (39.6)	88 (27.8)
Hypertension	33 (10.4)	22 (6.9)

(continued)

Table 9: Common AEs (in the SOC or in the PT ≥ 10% in at least one study arm) – RCT, direct comparison: elotuzumab + lenalidomide + low-dose dexamethasone vs. lenalidomide + low-dose dexamethasone (continued)

Study	**Patients with event[b] n (%)**	
SOC[a] **PT[a]**	**E-Ld** **N = 318**	**Ld** **N = 317**
ELOQUENT-2		
Injury, poisoning and procedural complications	115 (36.2)	88 (27.8)
Contusion	41 (12.9)	27 (8.5)
Eye disorders	101 (31.8)	79 (24.9)
Cataract	43 (13.5)	27 (8.5)
Renal and urinary disorders	78 (24.5)	58 (18.3)
Cardiac disorders	63 (19.8)	58 (18.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	50 (15.7)	33 (10.4)
Ear and labyrinth disorders	32 (10.1)	31 (9.8)

a: MedDRA version 18.0
b: Events that occurred during the treatment + 60 days follow-up.
AE: adverse event; E-Ld: elotuzumab + lenalidomide + dexamethasone; Ld: lenalidomide + dexamethasone; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 10: Common SAEs (in the SOC or in the PT ≥ 3% in at least one study arm) – RCT, direct comparison: elotuzumab + lenalidomide + low-dose dexamethasone vs. lenalidomide + low-dose dexamethasone

Study	**Patients with event[b] n (%)**	
SOC[a] **PT[a]**	**E-Ld** **N = 318**	**Ld** **N = 317**
ELOQUENT-2		
Overall rate of SAEs	223 (70.1)	190 (59.9)
Infections and infestations	114 (35.8)	84 (26.5)
Pneumonia	41 (12.9)	31 (9.8)
Respiratory tract infection	10 (3.1)	4 (1.3)
General disorders and administration site conditions	49 (15.4)	31 (9.8)
Fever	23 (7.2)	16 (5.0)
Progression of a disease	15 (4.7)	10 (3.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	37 (11.6)	31 (9.8)
Respiratory, thoracic and mediastinal disorders	33 (10.4)	22 (6.9)
Pulmonary embolism	10 (3.1)	8 (2.5)
Blood and lymphatic system disorders	22 (6.9)	17 (5.4)
Anaemia	10 (3.1)	7 (2.2)
Gastrointestinal disorders	20 (6.3)	24 (7.6)
Cardiac disorders	17 (5.3)	24 (7.6)
Injury, poisoning and procedural complications	17 (5.3)	20 (6.3)
Musculoskeletal and connective tissue disorders	17 (5.3)	18 (5.7)
Nervous system disorders	17 (5.3)	16 (5.0)
Renal and urinary disorders	17 (5.3)	19 (6.0)
Vascular disorders	15 (4.7)	11 (3.5)
Metabolism and nutrition disorders	13 (4.1)	10 (3.2)
Hepatobiliary disorders	11 (3.5)	1 (0.3)

a: MedDRA version 18.0
b: Events that occurred during the treatment + 60 days follow-up.
E-Ld: elotuzumab + lenalidomide + dexamethasone; Ld: lenalidomide + dexamethasone; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse events; SOC: System Organ Class; vs.: versus

Table 11: Common AEs with CTCAE grade 3 or 4 (in the SOC or in the PT ≥ 5% in at least one study arm) – RCT, direct comparison: elotuzumab + lenalidomide + low-dose dexamethasone vs. lenalidomide + low-dose dexamethasone

Study	**Patients with event[b] n (%)**	
SOC[a] **PT[a]**	**E-Ld** **N = 318**	**Ld** **N = 317**
ELOQUENT-2		
Overall rate of AEs with CTCAE grade 3 or 4	248 (78.0)	212 (66.9)
General disorders and administration site conditions	67 (21.1)	51 (16.1)
Fatigue	29 (9.1)	26 (8.2)
Asthenia	16 (5.0)	12 (3.8)
Infections and infestations	100 (31.4)	78 (24.6)
Pneumonia	37 (11.6)	24 (7.6)
Gastrointestinal disorders	33 (10.4)	30 (9.5)
Diarrhoea	17 (5.3)	15 (4.7)
Musculoskeletal and connective tissue disorders	46 (14.5)	40 (12.6)
Back pain	17 (5.3)	14 (4.4)
Nervous system disorders	36 (11.3)	29 (9.1)
Blood and lymphatic system disorders	138 (43.4)	144 (45.4)
Anaemia	49 (15.4)	52 (16.4)
Neutropenia	81 (25.5)	105 (33.1)
Thrombocytopenia	40 (12.6)	36 (11.4)
Lymphopenia	28 (8.8)	13 (4.1)
Respiratory, thoracic and mediastinal disorders	34 (10.7)	25 (7.9)
Metabolism and nutrition disorders	67 (21.1)	52 (16.4)
Hyperglycaemia	23 (7.2)	15 (4.7)
Hypokalaemia	17 (5.3)	16 (5.0)
Investigations	36 (11.3)	33 (10.4)
Psychiatric disorders	19 (6.0)	14 (4.4)
Vascular disorders	33 (10.4)	25 (7.9)
Deep vein thrombosis	20 (6.3)	8 (2.5)
Eye disorders	30 (9.4)	18 (5.7)
Cataract	24 (7.5)	16 (5.0)
Cardiac disorders	15 (4.7)	22 (6.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	27 (8.5)	17 (5.4)

a: MedDRA version 18.0
b: Events that occurred during the treatment + 60 days follow-up.
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; E-Ld: elotuzumab + lenalidomide + dexamethasone; Ld: lenalidomide + dexamethasone; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 12: Common discontinuations due to AEs (in the SOC or in the PT ≥ 1% in at least one study arm) – RCT, direct comparison: elotuzumab + lenalidomide + low-dose dexamethasone vs. lenalidomide + low-dose dexamethasone

Study	**Patients with event[b] n (%)**	
SOC[a] **PT[a]**	**E-Ld** **N = 318**	**Ld** **N = 317**
ELOQUENT-2		
Overall rate of discontinuations due to AEs	96 (30.2)	94 (29.7)
General disorders and administration site conditions	21 (6.6)	20 (6.3)
Progression of a disease	12 (3.8)	4 (1.3)
Asthenia	2 (0.6)	4 (1.3)
Fatigue	2 (0.6)	5 (1.6)
General physical health deterioration	2 (0.6)	5 (1.6)
Infections and infestations	15 (4.7)	15 (4.7)
Sepsis	2 (0.6)	4 (1.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	14 (4.4)	8 (2.5)
Nervous system disorders	11 (3.5)	14 (4.4)
Blood and lymphatic system disorders	10 (3.1)	12 (3.8)
Anaemia	3 (0.9)	4 (1.3)
Neutropenia	1 (0.3)	5 (1.6)
Thrombocytopenia	1 (0.3)	6 (1.9)
Vascular disorders	8 (2.5)	0 (0)
Psychiatric disorders	7 (2.2)	3 (0.9)
Respiratory, thoracic and mediastinal disorders	7 (2.2)	6 (1.9)
Metabolism and nutrition disorders	6 (1.9)	4 (1.3)
Cardiac disorders	5 (1.6)	5 (1.6)
Gastrointestinal disorders	5 (1.6)	7 (2.2)
Investigations	5 (1.6)	2 (0.6)
Musculoskeletal and connective tissue disorders	5 (1.6)	4 (1.3)
Renal and urinary disorders	5 (1.6)	5 (1.6)
Skin and subcutaneous tissue disorders	4 (1.3)	3 (0.9)

a: MedDRA version 18.0
b: Discontinuation of at least one treatment component.
AE: adverse event; E-Ld: elotuzumab + lenalidomide + dexamethasone; Ld: lenalidomide + dexamethasone; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Appendix B – Kaplan-Meier curves on results of the ELOQUENT-2 study (if available)

Outcome "overall survival"

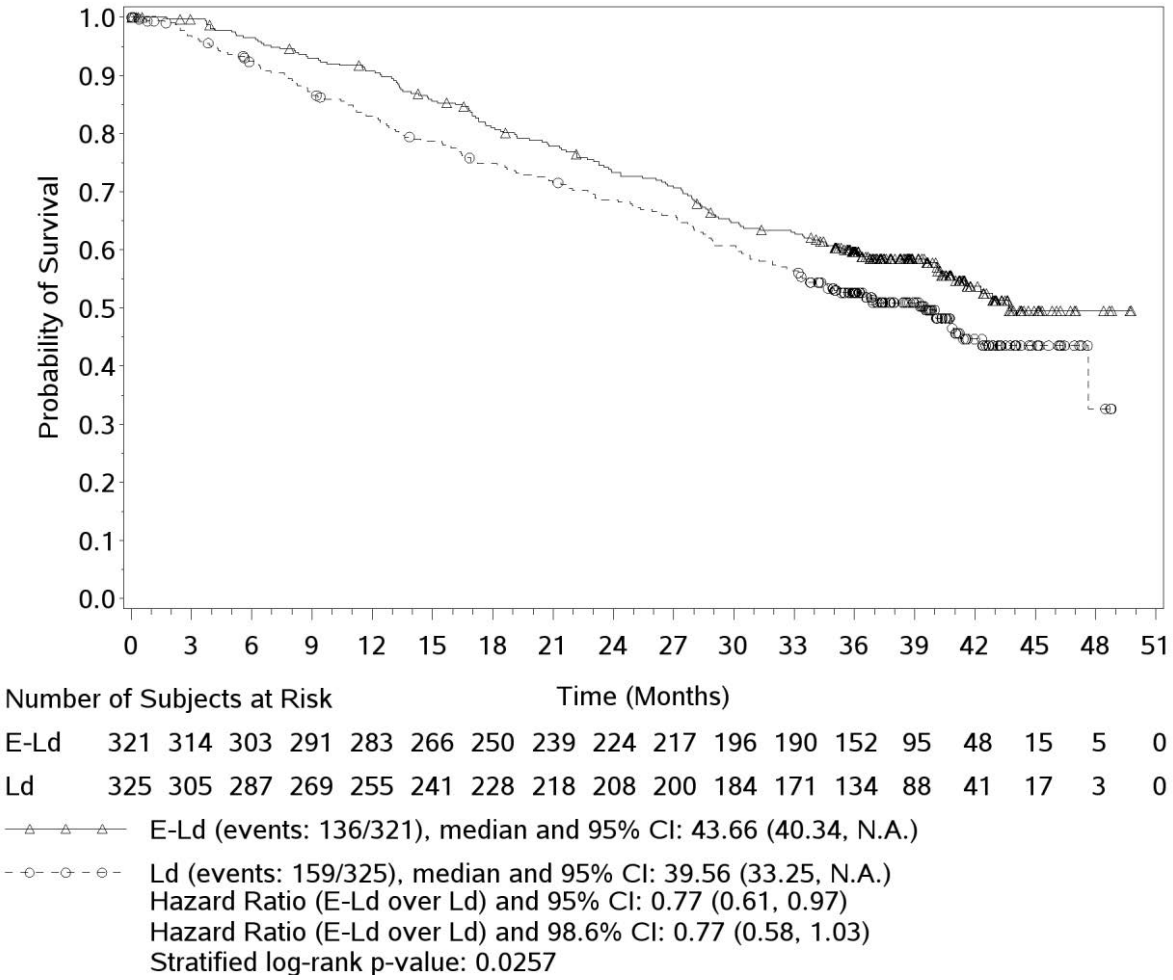

Figure 1: Kaplan-Meier curve for the outcome "all-cause mortality" – RCT, direct comparison: elotuzumab + lenalidomide + low-dose dexamethasone vs. lenalidomide + low-dose dexamethasone (data cut-off: 29 October 2015)