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Pomalidomide (multiple myeloma) –

Addendum to Commission A19-50[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Event
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
SGB	Sozialgesetzbuch (Social Code Book)
ISS	International Staging System
PT	Preferred Term
SAE	serious adverse event
SOC	System Organ Class

1 Background

On 29 October 2019, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A19-50 (Pomalidomide – Benefit assessment according to §35a Social Code Book V) [1].

With its dossier [2], the company presented the study MM-007 for the benefit assessment of pomalidomide in multiple myeloma. This study is relevant for the present therapeutic indication and was included in the benefit assessment of pomalidomide. However, the analyses on the outcome category "side effects" were incomplete.

With its written comments on the dossier assessment, the company presented further analyses of study MM-007 [3,4]. The G-BA commissioned IQWiG to assess the following analyses:

- Event time analyses on adverse events (AEs) at System Organ Class (SOC) and/or Preferred Term (PT) level
- Event time analyses on AEs for subgroups

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

2 Assessment

2.1 Analyses subsequently submitted

The written comments of the company [3] contained the following analyses relevant for the assessment:

- Event time analyses of the SOCs and PTs of all AEs (irrespective of the severity grade)
- Event time analyses of the SOCs of the severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3) which occurred in ≥ 5% of the patients in ≥ 1 treatment arm
- Event time analyses of the SOCs of the SAEs which occurred in ≥ 2% of the patients in ≥ 1 treatment arm
- Subgroup analyses of the overall rates of the severe AEs (CTCAE grade ≥ 3) and the SAEs for the potential effect modifiers included in the dossier assessment [1]

These results were used for the choice of further specific AEs (see Section 2.2) and the investigation of further potential effect modifications (see Section 2.3). Under overall consideration of the results at outcome level, the added benefit was then derived from the dossier and the results subsequently submitted (see Section 2.4) and presented across outcomes (see Section 2.5).

A presentation of the common AEs, SAEs and severe AEs (CTCAE grade ≥ 3) according to SOC and PT is found in Appendix C of the dossier assessment on pomalidomide [1].

2.2 Results

The results subsequently submitted by the company in its comments enable the identification of further specific AEs (for information on the approach in the choice of specific AEs see dossier assessment on pomalidomide) [1].

Table 1 shows specific AEs identified on the basis of the analyses subsequently submitted by the company. The Kaplan-Meier curves on the specific AEs identified subsequently are presented in Appendix A. The figures on the subgroup analyses are found in Appendix B.

Table 1: Results (side effects) – RCT, direct comparison: pomalidomide + bortezomib + dexamethasone vs. bortezomib + dexamethasone

Study Outcome category Outcome	Pomalidomide + bortezomib + dexamethasone		Bortezomib + dexamethasone		Pomalidomide + bortezomib + dexamethasone vs. bortezomib + dexamethasone
	N[a]	Median time to event in months [95% CI][b] patients with event n (%)	N[a]	Median time to event in months [95% CI][b] patients with event n (%)	HR [95% CI]; p-value[c]
MM-007					
Side effects (second data cut-off 15 September 2018)					
Cataract (PT, AE)	278	48.6 [NC; NC] 18 (6.5)	270	NA 2 (0.7)	5.61 [1.28; 24.63] 0.022
Constipation (PT, AE)	278	36.8 [36.8; 53.2] 105 (37.8)	270	NA 66 (24.4)	1.53 [1.12; 2.08] 0.007
Stomatitis (PT, AE)	278	NA 17 (6.1)	270	NA 1 (0.4)	15.70 [2.09; 117.9] 0.007
Oedema peripheral (PT, AE)	278	38.8 [24.1; NC] 99 (35.6)	270	NA 54 (20.0)	1.63 [1.17; 2.27] 0.004
Fever (PT, AE)	278	45.4 [NC; NC] 72 (25.9)	270	NA 33 (12.2)	1.73 [1.14; 2.62] 0.010
Muscular weakness (PT, AE)	278	NA 39 (14.0)	270	NA 13 (4.8)	2.58 [1.37; 4.84] 0.003
Tremor (PT, AE)	278	NA 31 (11.2)	270	NA 8 (3.0)	3.56 [1.64; 7.75] 0.001
Pulmonary embolism (PT, AE)	278	NA 11 (4.0)	270	NA 1 (0.4)	8.22 [1.05; 64.04] 0.044
Rash (PT, AE)	278	NA 29 (10.4)	270	NA 9 (3.3)	2.55 [1.20; 5.42] 0.015
Blood and lymphatic system disorders (SOC, severe AEs [CTCAE grade ≥ 3])	278	4.2 [1.8; 12.9] 163 (58.6)	270	NA [14.8; NC] 112 (41.5)	1.48 [1.16; 1.88] 0.002
Infections and infestations (SOC, SAE)	278	NA [18.3; NC] 98 (35.3)	270	NA [31.3; NC] 50 (18.5)	1.61 [1.14; 2.26] 0.007

a: Safety population.
b: Institute's calculation (conversion from weeks to months).
c: Cox proportional hazards model.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; n: number of patients with event; N: number of analysed patients (ITT population); NA: not achieved; NC: not calculable; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

As in the dossier assessment [1], the risk of bias of the subsequently submitted results on the outcome category "side effects" was rated as high. At most hints, e.g. of an added benefit, can therefore be derived from the results of the MM-007 study that were subsequently submitted.

Side effects

Specific AEs

AEs

On the basis of all AEs, irrespective of the severity grade, a statistically significant disadvantage of pomalidomide + bortezomib + dexamethasone was shown for the outcomes "cataract (PT, AE)", "obstipation (PT, AE)", "stomatitis (PT, AE)", "oedema peripheral (PT, AE)", "fever (PT, AE)", "muscular weakness (PT, AE)", "tremor (PT, AE)", "pulmonary embolism (PT, AE)" and "rash (PT, AE)". In each case, this resulted in a hint of greater harm from pomalidomide + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone.

SAEs

Based on the SAEs, there is a statistically significant disadvantage of pomalidomide + bortezomib + dexamethasone for the outcome "infections and infestations (SOC, SAE)". This resulted in a hint of greater harm from pomalidomide + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone.

The disadvantage in the SOC "infections and infestations" also applies to the severe AEs (CTCAE grade ≥ 3).

Severe AEs (CTCAE grade ≥ 3)

On the basis of the severe AEs (CTCAE grade ≥ 3), a statistically significant disadvantage of pomalidomide + bortezomib + dexamethasone was shown for the outcome "blood and lymphatic system disorders" (SOC, severe AEs [CTCAE grade ≥ 3]). This resulted in a hint of greater harm from pomalidomide + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone.

2.3 Subgroup analyses

The check for further effect modifications was based on the same subgroup characteristics and the same methodology as in dossier assessment A19-50 [5].

The results subsequently submitted by the company do not allow a complete identification of the effect modifications for the relevant outcomes, since the subgroup analyses for the specific AEs, SAEs and severe AEs (CTCAE degree ≥ 3) are missing.

The subsequently submitted subgroup results of pomalidomide + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone are summarized in Table 2. The figures on the subgroup analyses are found in Appendix B.

Table 2: Subgroups (side effects) – RCT, direct comparison: pomalidomide + bortezomib + dexamethasone vs. bortezomib + dexamethasone

Study **Outcome** **Characteristic** **Subgroup**	**Pomalidomide + bortezomib + dexamethasone**		**Bortezomib + dexamethasone**		**Pomalidomide + bortezomib + dexamethasone vs. bortezomib + dexamethasone**	
	N	**Median time to event in months [95% CI]** **patients with event n (%)**	**N**	**Median time to event in months [95% CI]** **patients with event n (%)**	**HR [95% CI]**	**p-value[a]**
MM-007						
Side effects (second data cut-off 15 September 2018)						
Severe AEs (CTCAE grade ≥ 3)						
ISS stage						
I	*147*	*1.61 [0.82; 2.04]* *137 (93.2)*	*136*	*3.22 [2.10; 5.16]* *82 (60.3)*	*1.98 [1.51; 2.61]*	*< 0.001*
II	*85*	*0.72 [0.53; 1.18]* *77 (90.6)*	*86*	*1.08 [0.85; 1.74]* *68 (79.1)*	*1.33 [0.96; 1.85]*	*0.085*
III	*46*	*0.71 [0.36; 0.85]* *44 (95.7)*	*48*	*0.72 [0.36; 1.05]* *43 (89.6)*	*1.12 [0.74; 1.71]*	*0.591*
					Interaction:	*0.045[b]*
Severe AEs (CTCAE grade ≥ 3)						
ISS stage						
I	147	1.61 [0.82; 2.04] 137 (93.2)	136	3.22 [2.10; 5.16] 82 (60.3)	1.98 [1.51; 2.61]	< 0.001
II or III	131	ND 121 (92.4)	134	ND 111 (82.8)	1.25 [0.96; 1.61]	0.095
					Interaction:	0.016[c]

a: Cox proportional hazards model with treatment arm and baseline score as covariates, adjusted by the stratification factors age, number of prior anti-myeloma regimens and beta-2 microglobulin level at screening.
b: Cox model with terms for the subgroup, the treatment group and the subgroup-treatment interaction.
c: Institute's calculation: meta-analysis of the subgroup results for ISS stages II and III (fixed-effect model).
AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; ISS: International Staging System; n: number of patients with event; N: number of analysed patients; RCT: randomized controlled trial; vs.: versus

For the overall rate of severe AEs (CTCAE degree ≥ 3), an effect modification results from the characteristic "ISS stage" with subgroups I, II and III. In the present data situation, the subgroups with homogeneous effects (ISS stages II and III) were aggregated (see Figure 15 in Appendix B).

There was no statistically significant difference between the treatment arms of the subgroup aggregated from ISS stages II and III. A statistically significant difference to the disadvantage

of pomalidomide + bortezomib + dexamethasone was shown for the subgroup of patients in ISS stage I. This resulted in a hint of greater harm for patients in ISS stage I. For patients in ISS stage II or III, there is no hint of greater harm from pomalidomide + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone at the level of the overall rate of severe AEs (CTCAE grade ≥ 3).

Since - as mentioned above - the subgroup analyses for the specific AEs are missing, the significance of the present effect modification can only be assessed to a limited extent.

2.4 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Sections 2.2 and 2.3 (see Table 3). In Table 3, the new results provided in the company's comments are printed in **bold**.

Determination of the outcome category for the outcomes on side effects

It cannot be inferred from the dossier and from the company's comments for all outcomes considered in the present benefit assessment, whether they were serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

The specific AE "pulmonary embolism (PT, AE)" is assigned to the category serious/severe side effects, because all affected patients had ≥ 1 severe AE (CTCAE grade ≥ 3) "pulmonary embolism".

The specific AEs "cataract (PT, AE)", "constipation (PT, AE)", "stomatitis (PT, AE)", "peripheral oedema (PT, AE)", "fever (PT, AE)", "muscular weakness (PT, AE)", "tremor (PT, AE)" and rash (PT, AE) are assigned to the category non-serious/non-severe side effects, because less than 50% of the events were SAEs or severe AEs (CTCAE grade ≥ 3).

Table 3: Extent of added benefit at outcome level: pomalidomide + bortezomib + dexamethasone vs. bortezomib + dexamethasone

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pomalidomide + bortezomib + dexamethasone vs. bortezomib + dexamethasone** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	40.5 vs. 30.5 HR: 0.91 [0.70; 1.18] p = 0.476	Lesser benefit/added benefit not proven
Morbidity		
Symptoms (EORTC QLQ-C30 symptom scales), time to deterioration by ≥ 10 points		
Fatigue	1.6 vs. 1.7 HR: 1.13 [0.92; 1.40] p = 0.241	Lesser benefit/added benefit not proven
Nausea and vomiting	10.6 vs. 13.9 HR: 1.05 [0.78; 1.41] p = 0.733	Lesser benefit/added benefit not proven
Pain	3.6 vs. 3.4 HR: 0.97 [0.76; 1.23] p = 0.782	Lesser benefit/added benefit not proven
Dyspnoea	3.5 vs. 3.5 HR: 1.14 [0.89; 1.45] p = 0.310	Lesser benefit/added benefit not proven
Insomnia	4.5 vs. 3.5 HR: 0.94 [0.73; 1.20] p = 0.598	Lesser benefit/added benefit not proven
Appetite loss	4.8 vs. 6.5 HR: 1.21 [0.93; 1.58] p = 0.152	Lesser benefit/added benefit not proven
Constipation	2.9 vs. 3.7 HR: 1.32 [1.03; 1.69] HR: 0.76 [0.59; 0.97][c] p = 0.030	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[d]
Diarrhoea	9.2 vs. 6.8 HR: 0.96 [0.72; 1.26] p = 0.752	Lesser benefit/added benefit not proven

(continued)

Table 3: Extent of added benefit at outcome level: pomalidomide + bortezomib + dexamethasone vs. bortezomib + dexamethasone (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pomalidomide + bortezomib + dexamethasone vs. bortezomib + dexamethasone** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Symptoms (EORTC QLQ-MY20 symptom scales), time to deterioration by ≥ 10 points		
Disease-related symptoms	7.9 vs. 11.0 HR: 1.08 [0.82; 1.42] p = 0.598	Lesser benefit/added benefit not proven
Side effects	3.0 vs. 3.0 HR: 1.07 [0.85; 1.35] p = 0.548	Lesser benefit/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 functional scales, time to deterioration by ≥ 10 points		
Global health status ISS stage I or II	ND vs. ND HR: 1.16 [0.90; 1.50] p = 0.251	Lesser benefit/added benefit not proven
III	5.3 vs. 1.5 HR: 0.47 [0.26; 0.87] p = 0.015 probability: "hint"	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ added benefit, extent: "considerable"
Physical functioning	3.3 vs. 3.6 HR: 1.12 [0.88; 1.42] p = 0.365	Lesser benefit/added benefit not proven
Role functioning	2.8 vs. 2.6 HR: 1.00 [0.80; 1.25] p = 0.987	Lesser benefit/added benefit not proven
Cognitive functioning	3.6 vs. 4.9 HR: 1.22 [0.95; 1.57] p = 0.117	Lesser benefit/added benefit not proven
Emotional functioning	4.5 vs. 5.1 HR: 1.12 [0.87; 1.43] p = 0.371	Lesser benefit/added benefit not proven

(continued)

Table 3: Extent of added benefit at outcome level: pomalidomide + bortezomib + dexamethasone vs. bortezomib + dexamethasone (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pomalidomide + bortezomib + dexamethasone vs. bortezomib + dexamethasone** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability[a]**	**Derivation of extent[b]**
Social functioning		
Number of prior anti-myeloma regimens		
1	2.8 vs. 5.5 HR: 1.63 [1.09; 2.43] HR: 0.61 [0.41; 0.92][c] p = 0.016 probability: "hint"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ lesser benefit, extent: "minor"
> 1	2.8 vs. 2.2 HR: 0.88 [0.66; 1.16] p = 0.351	Lesser benefit/added benefit not proven
EORTC QLQ-MY20 functional scales, time to deterioration by ≥ 10 points		
Future perspective	4.9 vs. 4.4 HR: 0.98 [0.76; 1.26] p = 0.861	Lesser benefit/added benefit not proven
Body image	5.0 vs. 6.9 HR: 0.98 [0.75; 1.27] p = 0.854	Lesser benefit/added benefit not proven
Side effects, time to first event		
SAEs	6.3 vs. 19.1 HR: 1.28 [1.01; 1.63] HR: 0.78 [0.61; 0.99][c] p = 0.039 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: "minor"
Severe AEs (CTCAE grade ≥ 3)		
ISS stage		
I	**1.6 vs. 3.2** **HR: 1.98 [1.51; 2.61]** **HR: 0.51 [0.38; 0.66][c]** **p < 0.001** **probability: "hint"**	**Outcome category: serious/severe side effects** **$CI_u < 0.75$, risk ≥ 5%** **greater harm, extent: "major"**
II or III	**ND** **HR: 1.25 [0.96; 1.61]** **p = 0.095**	**Greater/lesser harm not proven**

(continued)

Table 3: Extent of added benefit at outcome level: pomalidomide + bortezomib + dexamethasone vs. bortezomib + dexamethasone (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pomalidomide + bortezomib + dexamethasone vs. bortezomib + dexamethasone** **median time to event (months)** **effect estimation [95% CI]; p-value** **probability[a]**	**Derivation of extent[b]**
Discontinuation due to AEs (≥ 1 drug component)	37.3 vs. NA HR: 1.27 [0.90; 1.80] p = 0.173	Greater/lesser harm not proven
Specific AEs		
Peripheral neuropathy (SMQ, AE)	4.4 vs. 5.8 HR: 1.21 [0.95; 1.54] p = 0.115	Greater/lesser harm not proven
Venous thromboembolic event (SMQ, AE)	NA vs. NA HR: 3.27 [1.44; 7.44] HR: 0.31 [0.13; 0.69][c] p = 0.005 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% greater harm, extent: "major"
Neutropenia (PT, severe AEs [CTCAE grade ≥ 3])	18.0 vs. NA HR: 5.27 [3.40; 8.17] HR: 0.19 [0.12; 0.29][c] p < 0.001 probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% greater harm, extent: "major"
Cataract (PT, AE)	**48.6 vs. NA** **HR: 5.61 [1.28; 24.63]** **HR: 0.18 [0.04; 0.78][c]** **p = 0.022** **probability: "hint"**	**Outcome category: non-serious/non-severe side effects** **$CI_u < 0.80$** **greater harm, extent: "considerable"**
Constipation (PT, AE)	**36.8 vs. NA** **HR: 1.53 [1.12; 2.08]** **HR: 0.65 [0.48; 0.89][c]** **p = 0.007** **probability: "hint"**	**Outcome category: non-serious/non-severe side effects** **$0.80 \leq CI_u < 0.90$** **greater harm, extent: "minor"**
Stomatitis (PT, AE)	**NA vs. NA** **HR: 15.70 [2.09; 117.9]** **HR: 0.06 [0.01; 0.48][c]** **p = 0.007** **probability: "hint"**	**Outcome category: non-serious/non-severe side effects** **$CI_u < 0.80$** **greater harm, extent: "considerable"**
Oedema peripheral (PT, AE)	**38.8 vs. NA** **HR: 1.63 [1.17; 2.27]** **HR: 0.61 [0.44; 0.85][c]** **p = 0.004** **probability: "hint"**	**Outcome category: non-serious/non-severe side effects** **$0.80 \leq CI_u < 0.90$** **greater harm, extent: "minor"**

(continued)

Table 3: Extent of added benefit at outcome level: pomalidomide + bortezomib + dexamethasone vs. bortezomib + dexamethasone (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pomalidomide + bortezomib + dexamethasone vs. bortezomib + dexamethasone** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Fever (PT, AE)	**45.4 vs. NA** **HR: 1.73 [1.14; 2.62]** **HR: 0.58 [0.38; 0.88]**[c] **p = 0.010** **probability: "hint"**	**Outcome category: non-serious/non-severe side effects** **$0.80 \leq CI_u < 0.90$** **greater harm, extent: "minor"**
Muscular weakness (PT, AE)	**NA vs. NA** **HR: 2.58 [1.37; 4.84]** **HR: 0.39 [0.21; 0.73]**[c] **p = 0.003** **probability: "hint"**	**Outcome category: non-serious/non-severe side effects** **$CI_u < 0.80$** **greater harm, extent: "considerable"**
Tremor (PT, AE)	**NA vs. NA** **HR: 3.56 [1.64; 7.75]** **HR: 0.28 [0.13; 0.61]**[c] **p = 0.001** **probability: "hint"**	**Outcome category: non-serious/non-severe side effects** **$CI_u < 0.80$** **greater harm, extent: "considerable"**
Pulmonary embolism (PT, AE)	**NA vs. NA** **HR: 8.22 [1.05; 64.04]** **HR: 0.12 [0.02; 0.95]**[c] **p = 0.044** **probability: "hint"**	**Outcome category: serious/severe side effects** **$0.90 \leq CI_u < 1.00$** **greater harm, extent: "minor"**
Rash (PT, AE)	**NA vs. NA** **HR: 2.55 [1.20; 5.42]** **HR: 0.39 [0.18; 0.83]**[c] **p = 0.015** **probability: "hint"**	**Outcome category: non-serious/non-severe side effects** **$0.80 \leq CI_u < 0.90$** **greater harm, extent: "minor"**
Blood and lymphatic system disorders (SOC, severe AEs [CTCAE grade ≥ 3])	**4.2 vs. NA** **HR: 1.48 [1.16; 1.88]** **HR: 0.68 [0.53; 0.86]**[c] **p = 0.002** **probability: "hint"**	**Outcome category: serious/severe side effects** **$0.75 \leq CI_u < 0.90$** **greater harm, extent: "considerable"**
Infections and infestations (SOC, SAEs)	**NA vs. NA** **HR: 1.61 [1.14; 2.26]** **HR: 0.62 [0.44; 0.88]**[c] **p = 0.007** **probability: "hint"**	**Outcome category: serious/severe side effects** **$0.75 \leq CI_u < 0.90$** **greater harm, extent: considerable**

(continued)

Table 3: Extent of added benefit at outcome level: pomalidomide + bortezomib + dexamethasone vs. bortezomib + dexamethasone (continued)

a: Probability provided if there is a statistically significant and relevant effect.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
d: The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
Results presented in **bold** result from the company's written comments. All other results are already contained in the dossier assessment on pomalidomide.
AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; ISS: International Staging System; NA: not achieved; PT: preferred term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-MY20: Quality of Life Questionnaire-Multiple Myeloma Module 20; SAE: serious adverse event; SOC: system organ class; vs.: versus

2.5 Overall conclusion on added benefit

Table 4 summarizes the results considered in the overall conclusion on the extent of added benefit. In Table 4, the new results provided in the company's comments are printed in **bold**.

Table 4: Positive and negative effects from the assessment of pomalidomide + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone

Positive effects	**Negative effects**
Health-related quality of life ▪ EORTC QLQ-C30 functional scales, global health status ▫ ISS stage = III hint of added benefit – extent: "considerable"	Health-related quality of life ▪ EORTC QLQ-C30 – functional scales, social functioning ▫ number of prior anti-myeloma regimens = 1 hint of lesser benefit – extent: "minor"
–	Serious/severe side effects ▪ overall rate of SAEs: hint of greater harm – extent: "minor" ▪ specific SAEs: ▫ **infections and infestations (SOC, SAE): hint of greater harm – extent: "considerable"** ▪ overall rate of severe AEs (CTCAE grade ≥ 3): ▫ **ISS stage I: hint of greater harm – extent "major"** ▪ specific severe AEs (CTCAE grade ≥ 3): ▫ **blood and lymphatic system disorders (SOC), hint of greater harm – extent: "considerable",** including: - neutropenia (PT): indication of greater harm – extent: "major" ▪ specific AEs ▫ venous thromboembolic event (SMQ): hint of greater harm – extent "major" ▫ **pulmonary embolism (PT): hint of greater harm – extent: "minor"**
–	Non-serious/non-severe side effects ▪ specific AEs ▫ **cataract (PT), stomatitis (PT), muscular weakness (PT), tremor (PT), in each case hint of greater harm – extent: "considerable"** ▫ **constipation (PT), oedema peripheral (PT), fever (PT), rash (PT), in each case hint of greater harm – extent: "minor"**
The results presented in **bold** result from the analyses subsequently submitted by the company with its written comments. AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; ISS: International Staging System; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; QLQ-C30: Quality of Life Questionnaire-Core 30; SMQ: Standardized MedDRA Query; SAE: serious adverse event; SOC: system organ class; vs.: versus	

The analyses of the outcome category "side effects" subsequently submitted with the comments revealed further negative effects of pomalidomide + bortezomib + dexamethasone in comparison with bortezomib + dexamethasone. Moreover, an effect modification by the ISS stage was shown for the severe AEs (CTCAE degree ≥ 3); however, their impact is unclear as no subgroup analyses on specific AEs are available. Overall, the negative effects of pomalidomide + bortezomib + dexamethasone in comparison with bortezomib +

dexamethasone still outweighed the positive ones for all patients. On the basis of the available data, there is thus no change in the conclusion on the added benefit of dossier assessment A19-50.

2.6 Summary

The data subsequently submitted by the company in the commenting procedure did not change the conclusion on the added benefit of pomalidomide of dossier assessment A19-50.

Table 5 shows the result of the benefit assessment of pomalidomide under consideration of dossier assessment A19-50 and the present addendum.

Table 5: Pomalidomide – probability and extent of added benefit

Subindication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with multiple myeloma who had received at least one prior treatment regimen including lenalidomide	▪ 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 or ▪ carfilzomib in combination with lenalidomide and dexamethasone or ▪ carfilzomib in combination with dexamethasone or ▪ daratumumab in combination with lenalidomide and dexamethasone or ▪ daratumumab in combination with bortezomib and dexamethasone	Hint of lesser benefit
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**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The G-BA decides on the added benefit.

References

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

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2. Celgene. Pomalidomid (IMNOVID): Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 06.06.2019 [Accessed: 07.11.2019]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/467/#dossier.

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5. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10.07.2017 [Accessed: 01.07.2019]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

Appendix A – Kaplan-Meier curves

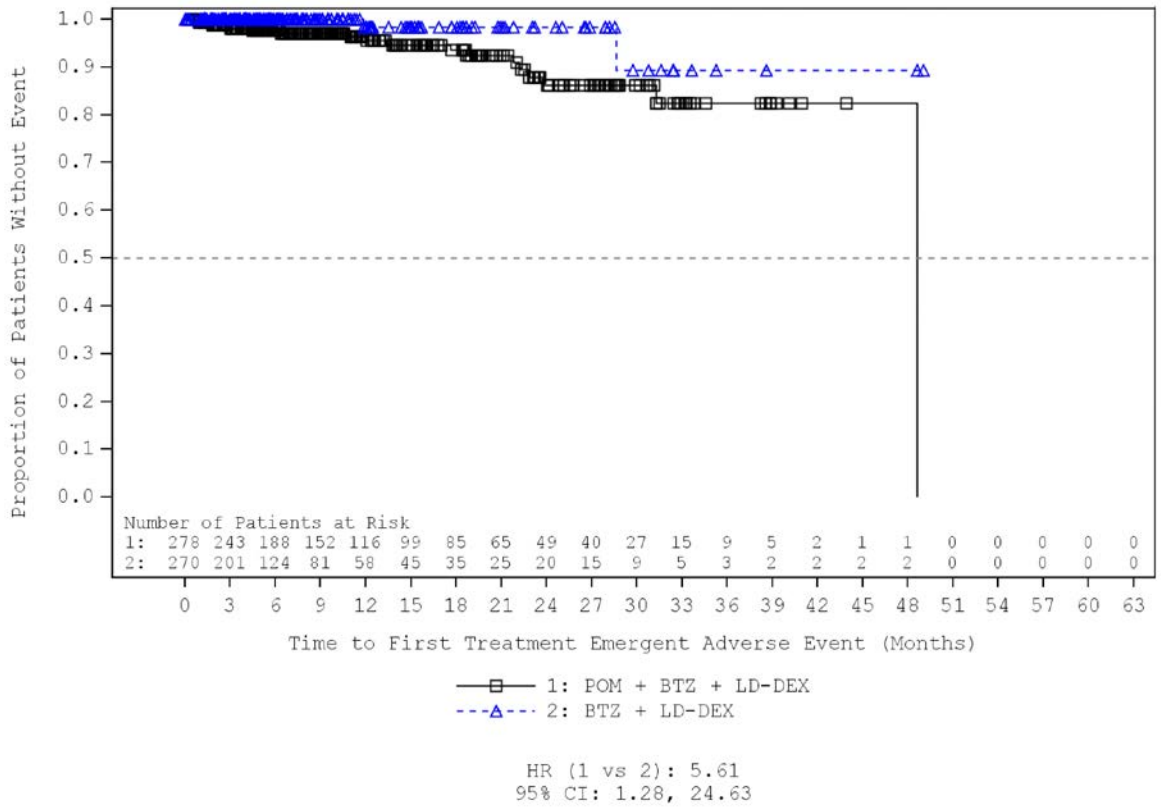

Figure 1: Kaplan-Meier curves on cataract (PT, AE) (study MM-007, data cut-off 2: 15 September 2018)

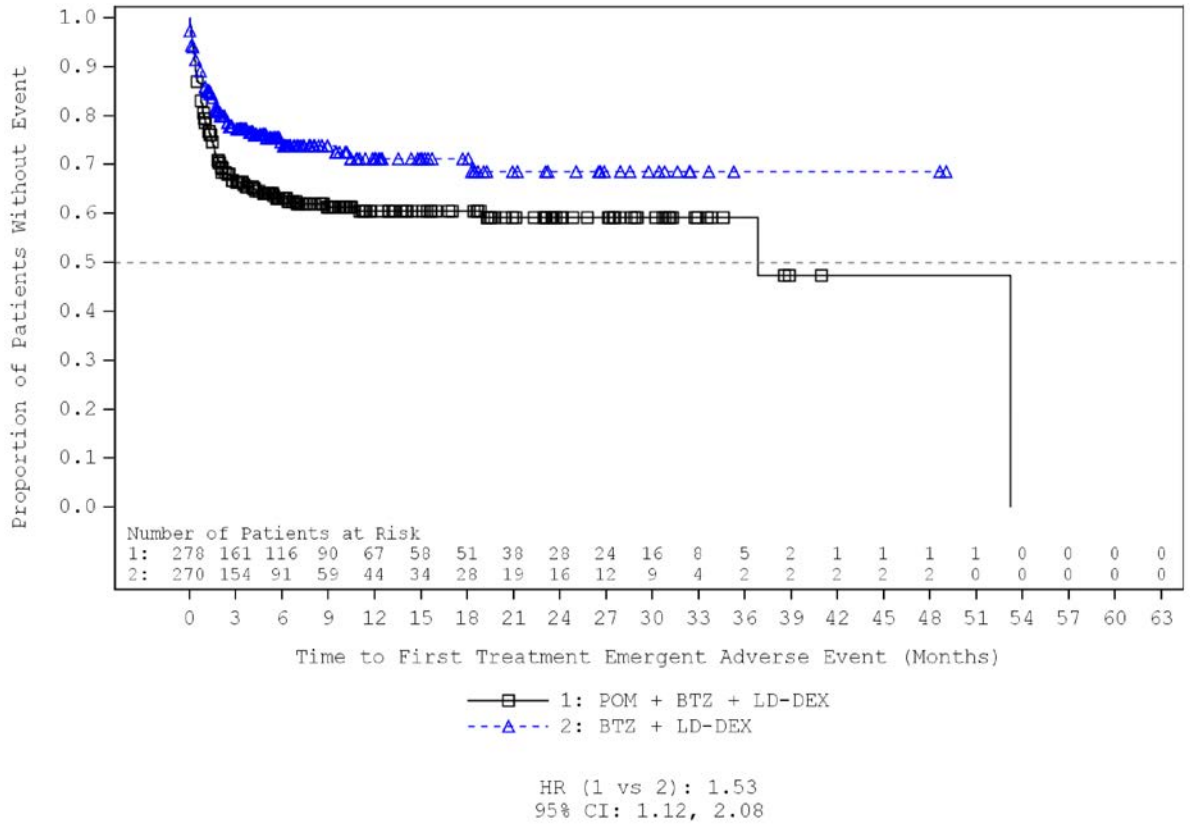

Figure 2: Kaplan-Meier curves on constipation (PT, AE) (study MM-007, data cut-off 2: 15 September 2018)

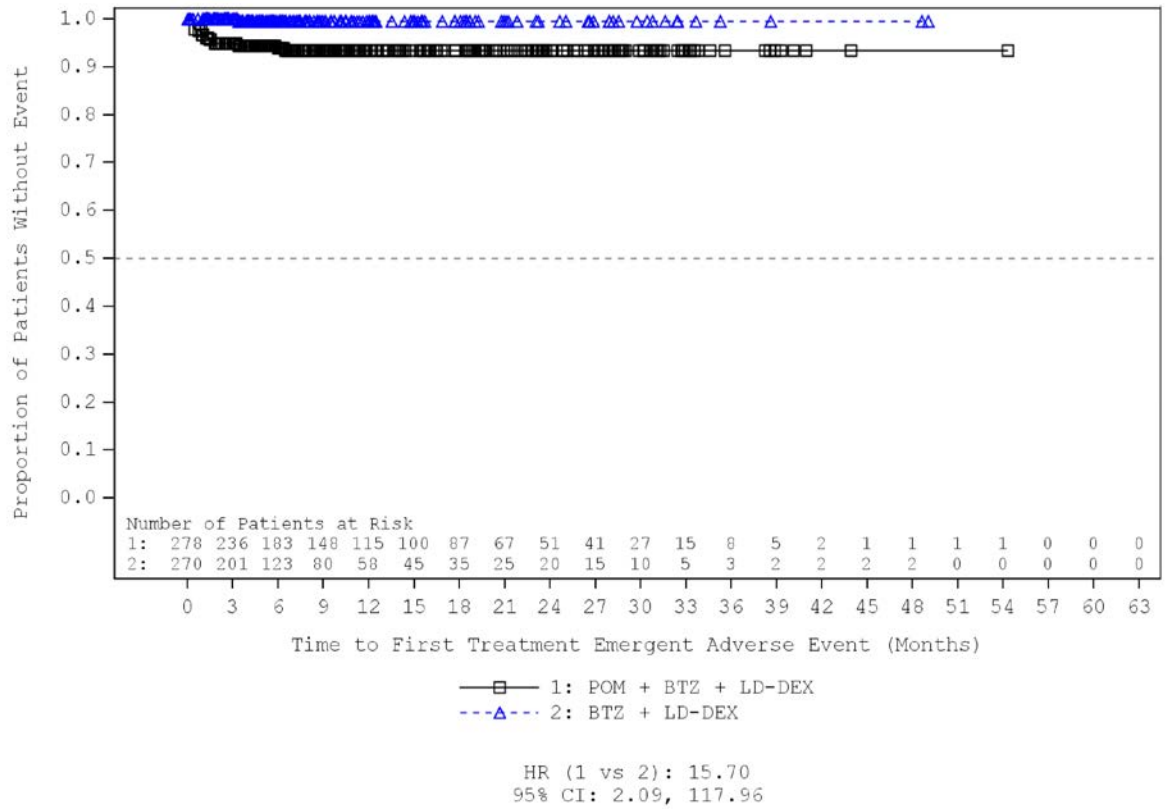

Figure 3: Kaplan-Meier curves on stomatitis (PT, UE) (study MM-007, data cut-off 2: 15 September 2018)

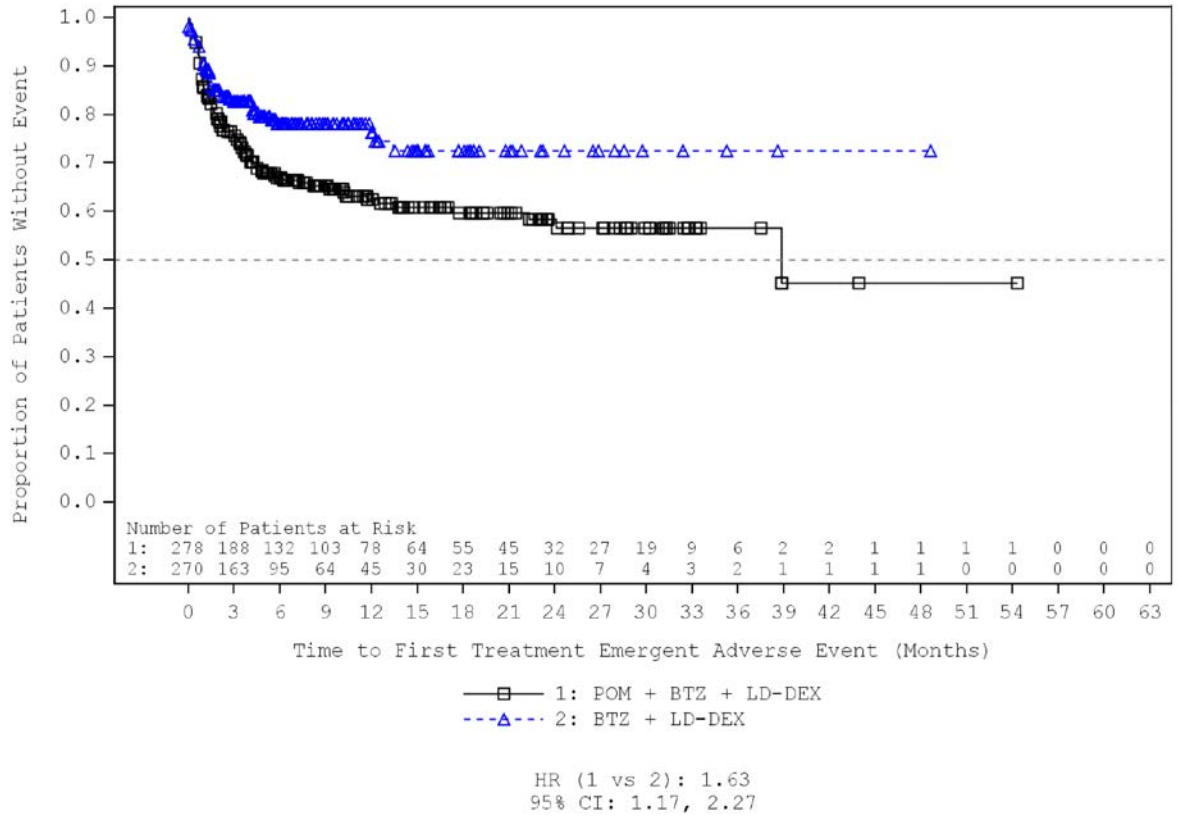

Figure 4: Kaplan-Meier curves on peripheral oedema (PT, AE) (study MM-007, data cut-off 2: 15 September 2018)

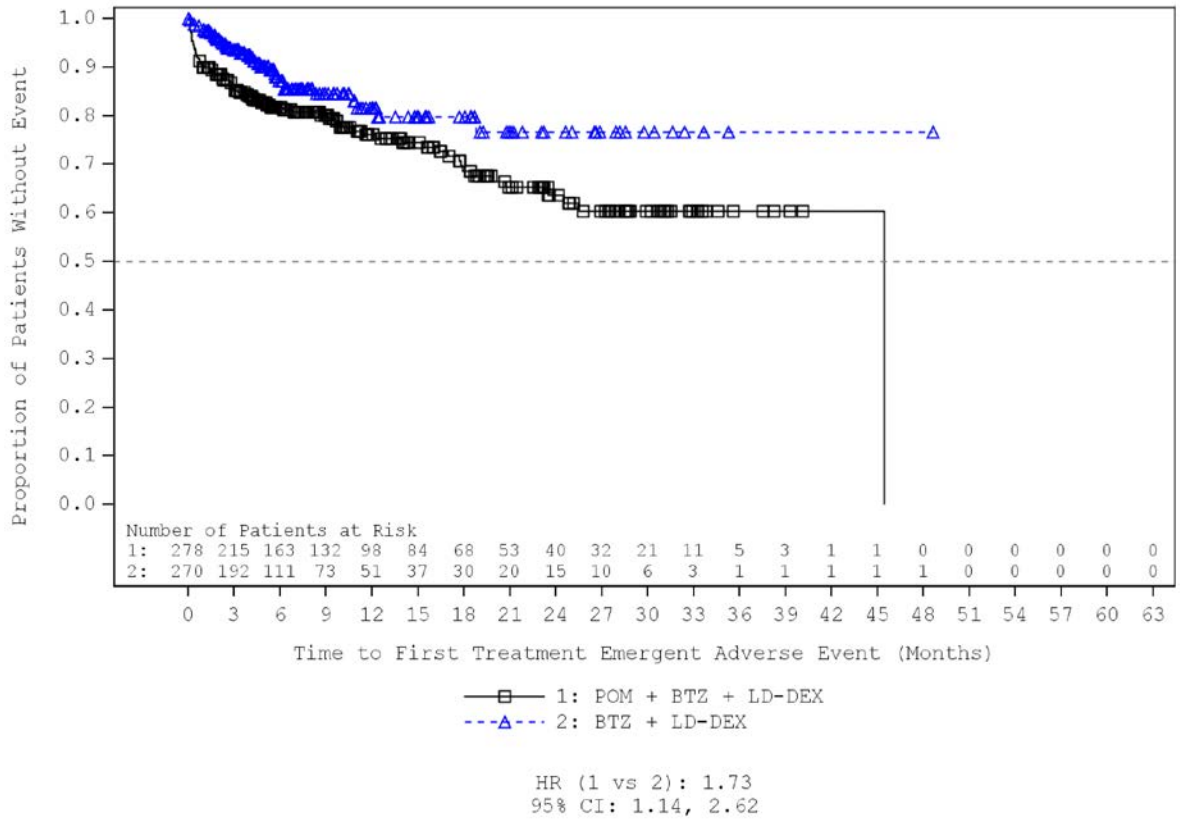

Figure 5: Kaplan-Meier curves on fever (PT, AE) (study MM-007, data cut-off 2: 15 September 2018)

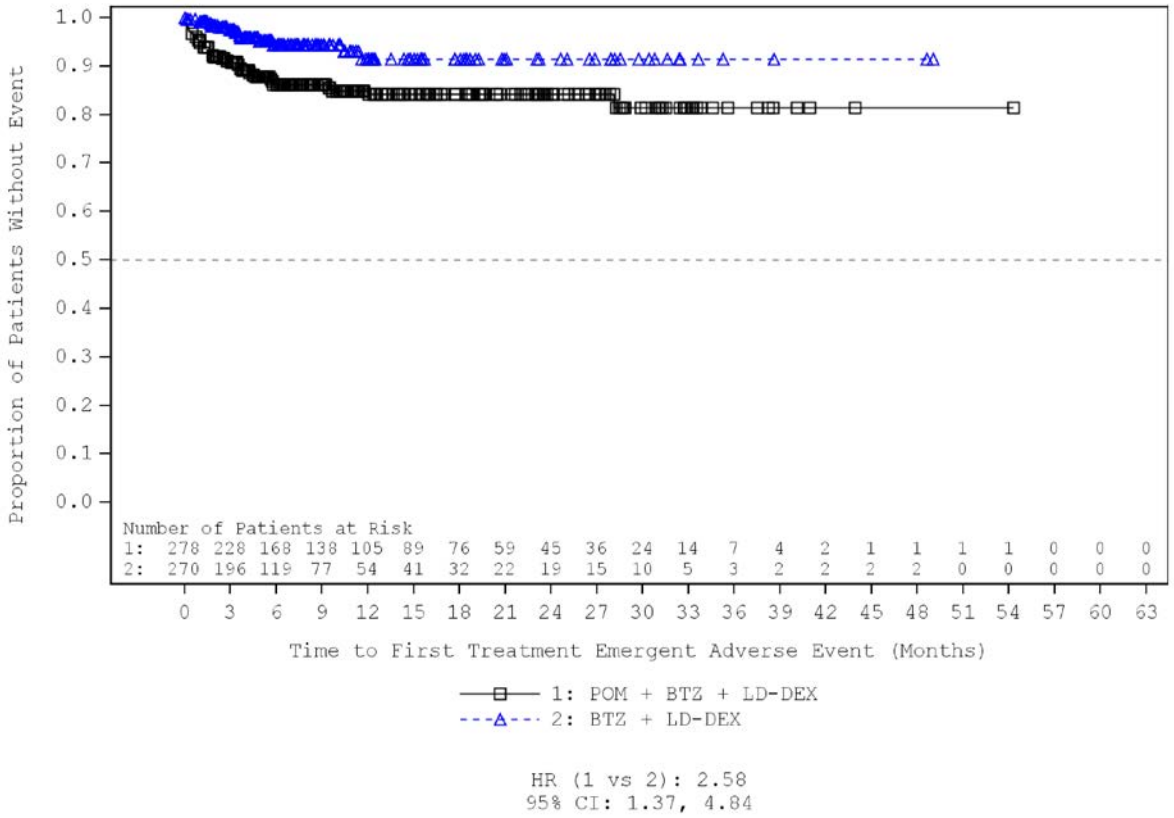

Figure 6: Kaplan-Meier curves on muscular weakness (PT, AE) (study MM-007, data cut-off 2: 15 September 2018)

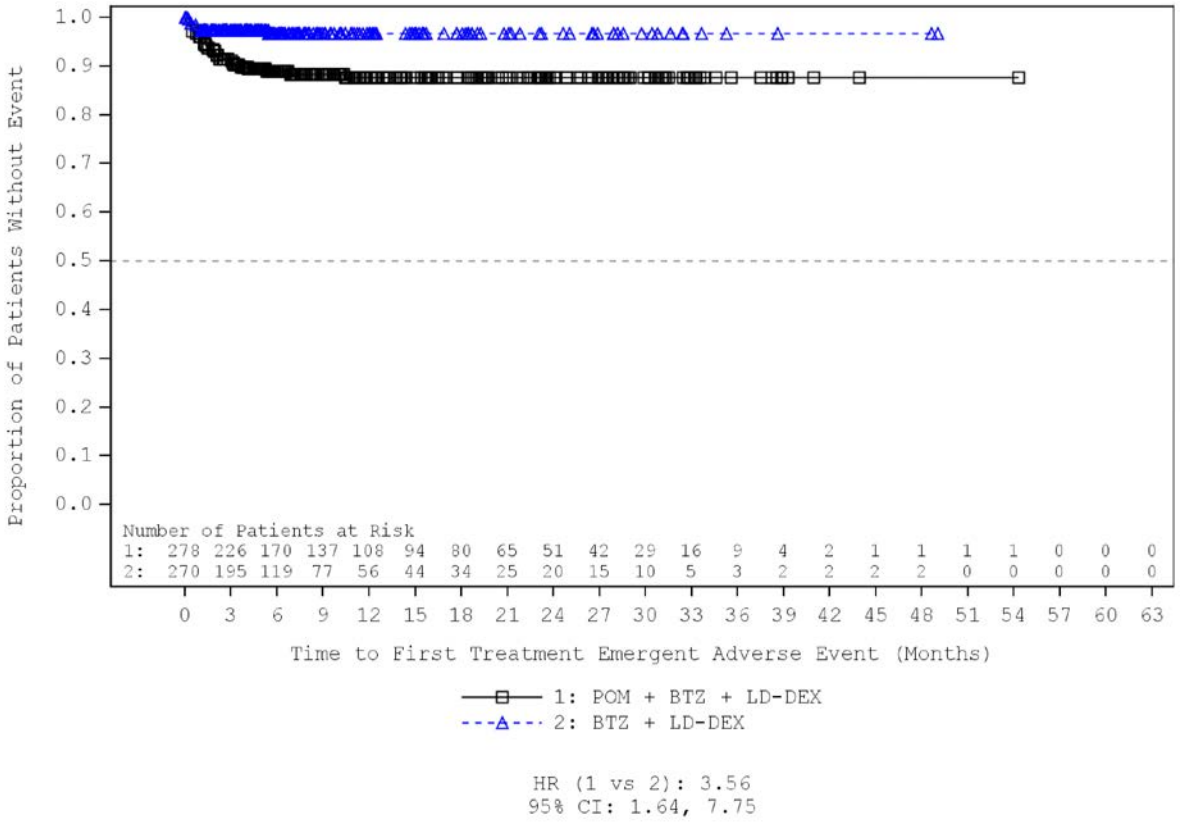

Figure 7: Kaplan-Meier curves on tremor (PT, AE) (study MM-007, data cut-off 2: 15 September 2018)

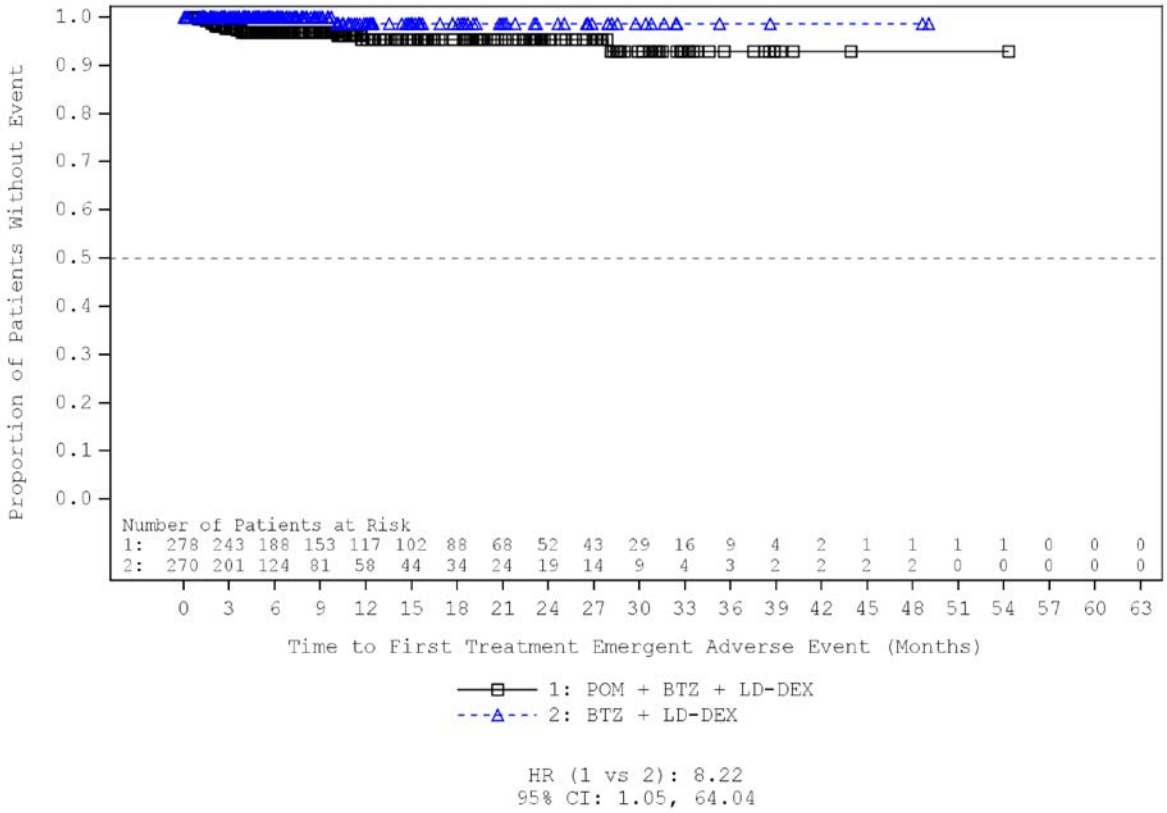

Figure 8: Kaplan-Meier curves on pulmonary embolism (PT, AE) (study MM-007, data cut-off 2: 15 September 2018)

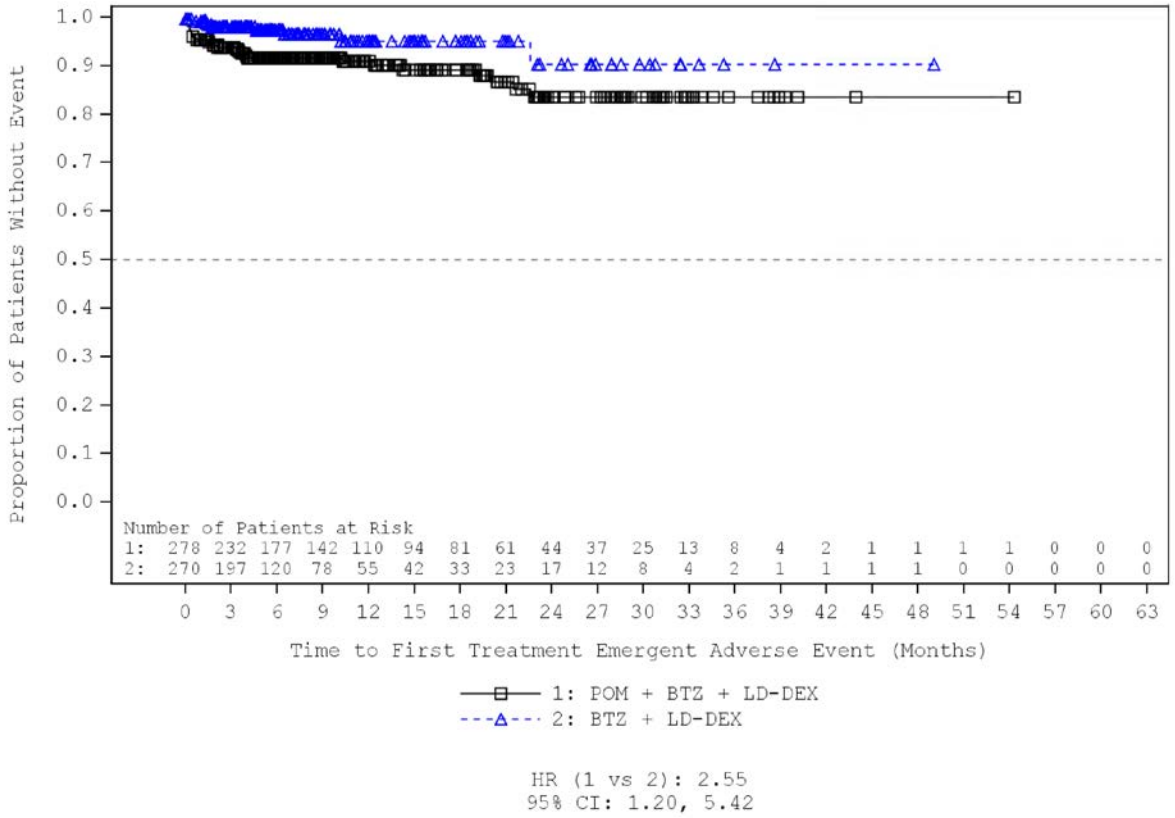

Figure 9: Kaplan-Meier curves on rash (PT, AE) (study MM-007, data cut-off 2: 15 September 2018

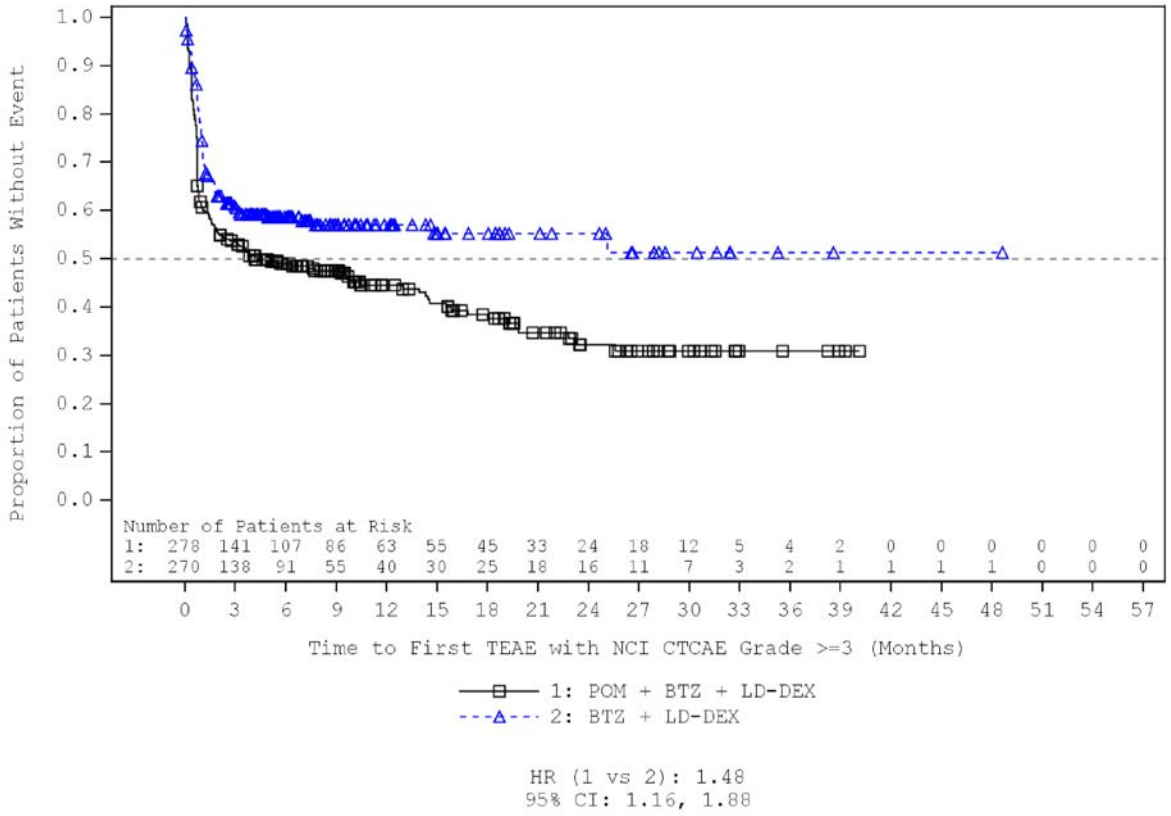

Figure 10: Kaplan-Meier curves on and lymphatic system disorders (SOC, severe AEs [CTCAE grade ≥ 3]) (study MM-007, data cut-off2: 15 September 2018)

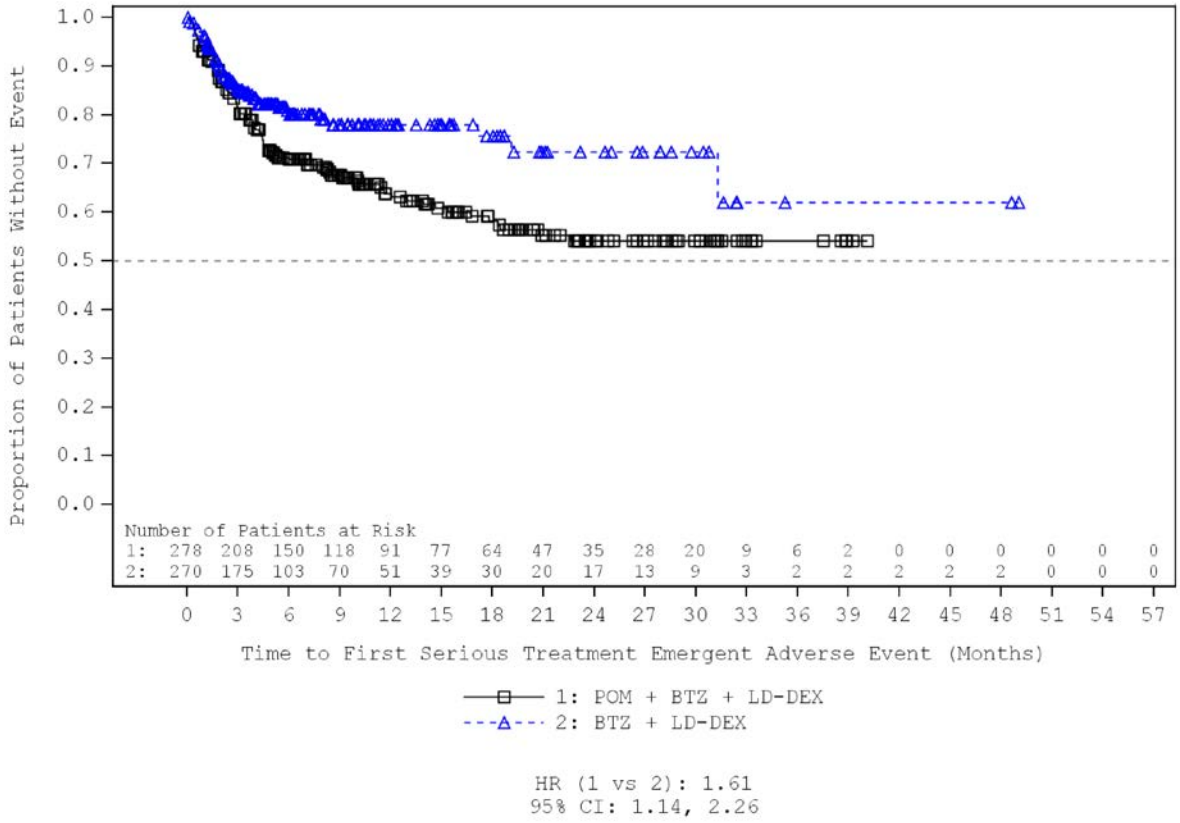

Figure 11: Kaplan-Meier curves on infections and infestations (SOC, SAEs) (study MM-007, data cut-off 2: 15 September 2018)

Appendix B – Subgroup analyses

B.1 – Kaplan-Meier curves

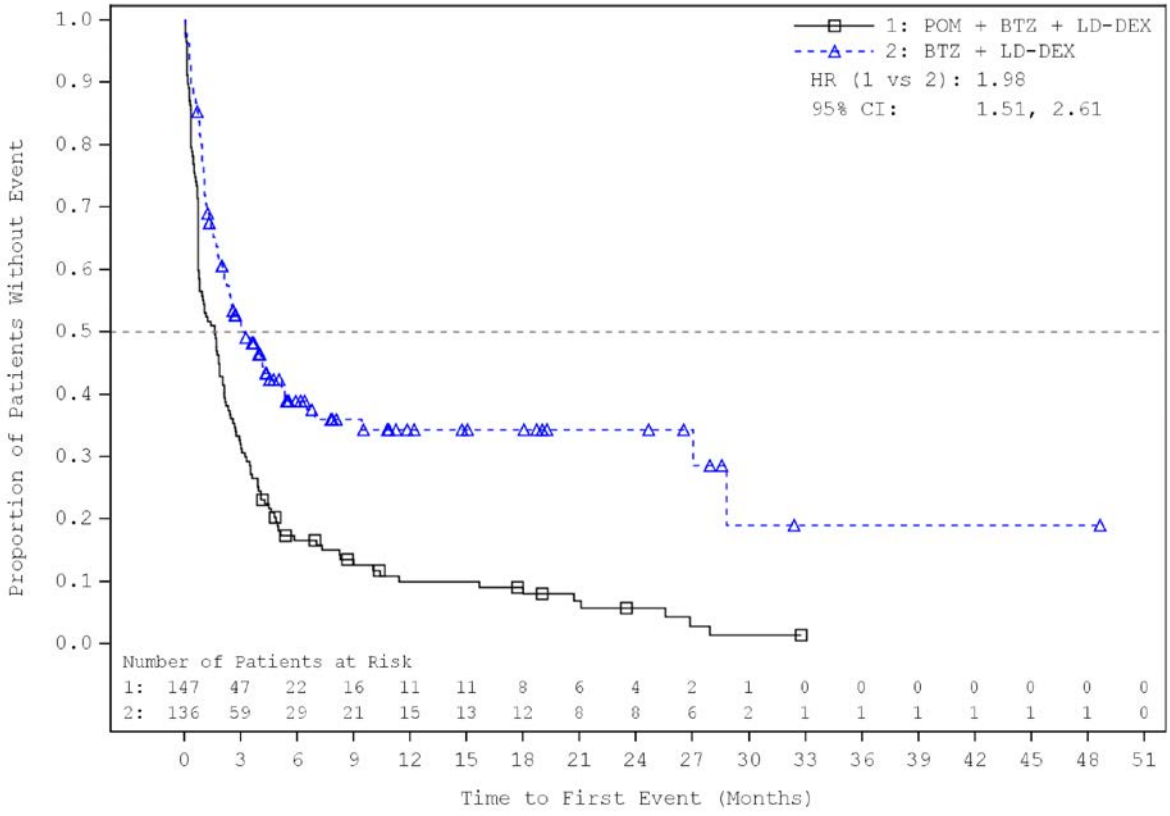

Figure 12: Kaplan-Meier curves on severe AEs (CTCAE grade ≥ 3), subgroup ISS stage = I (study MM-007, data cut-off 2: 15 September 2018)

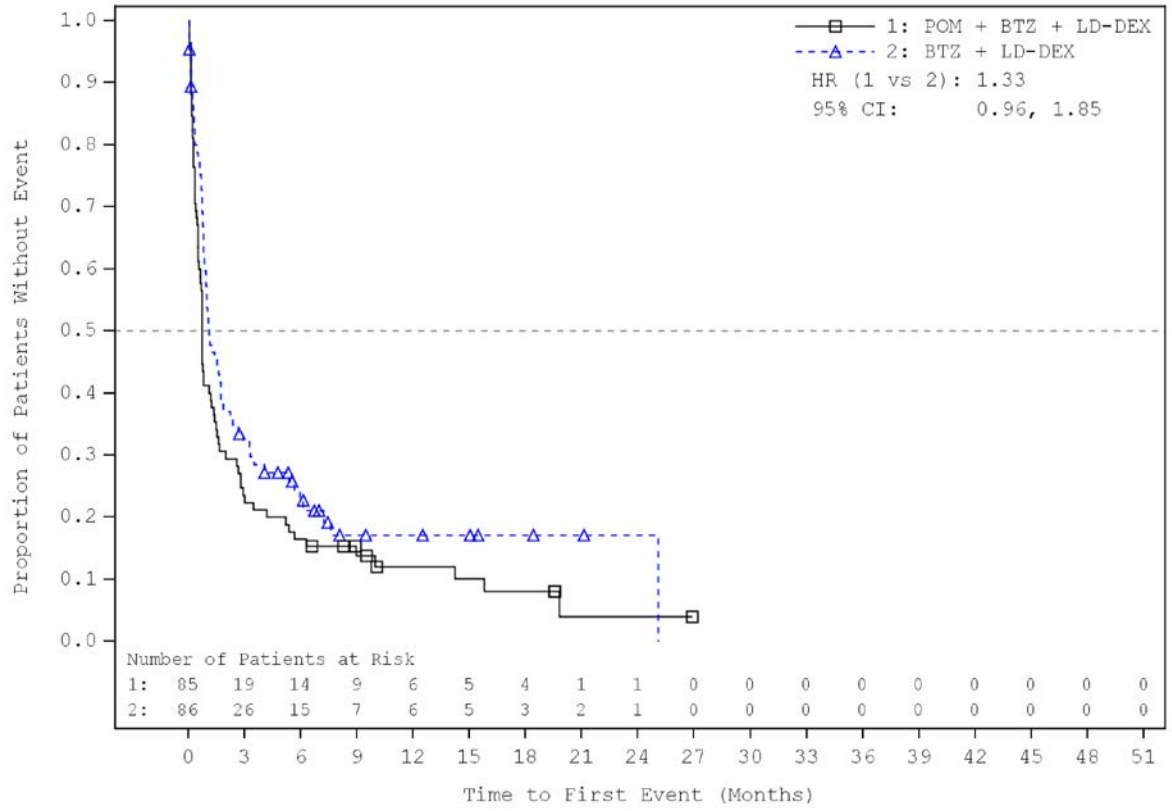

Figure 13: Kaplan-Meier curves on severe AEs (CTCAE grade ≥ 3), subgroup ISS stage = II (study MM-007, data cut-off 2: 15 September 2018)

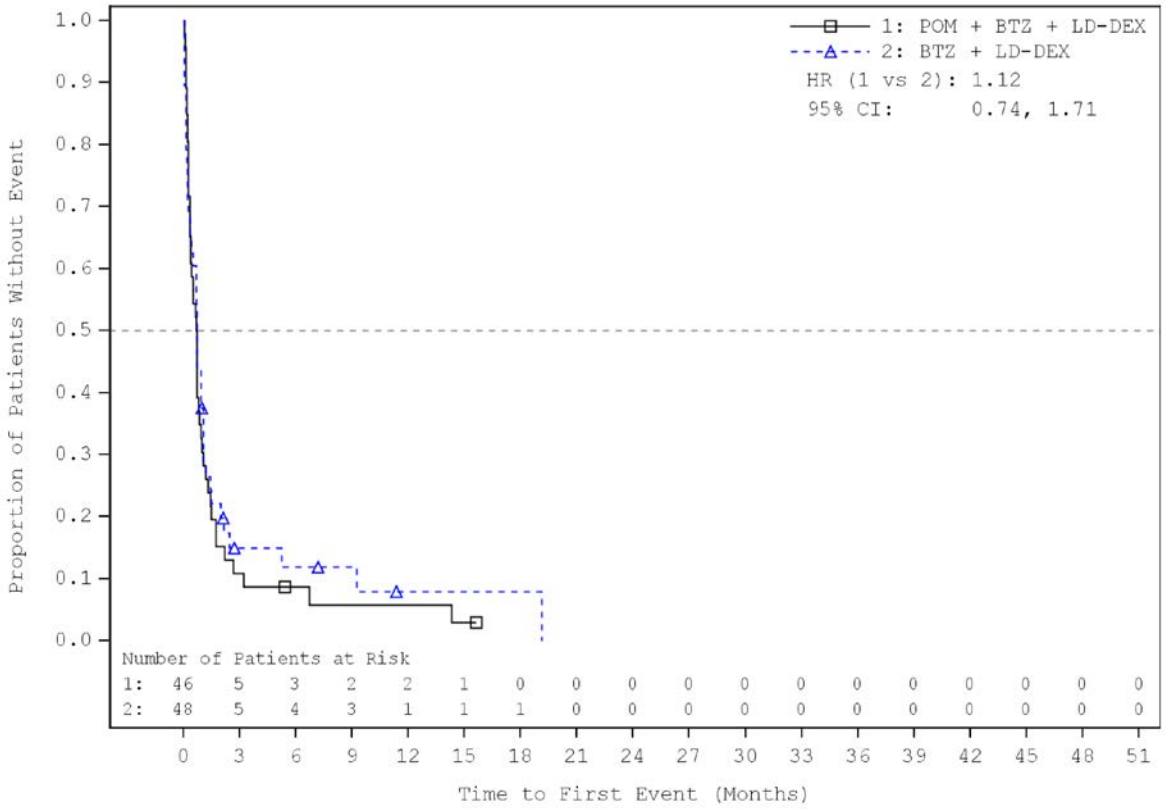

Figure 14: Kaplan-Meier curves on severe AEs (CTCAE grade ≥ 3), subgroup ISS stage = III (study MM-007, data cut-off 2: 15 September 2018)

B.2 – Forest Plot

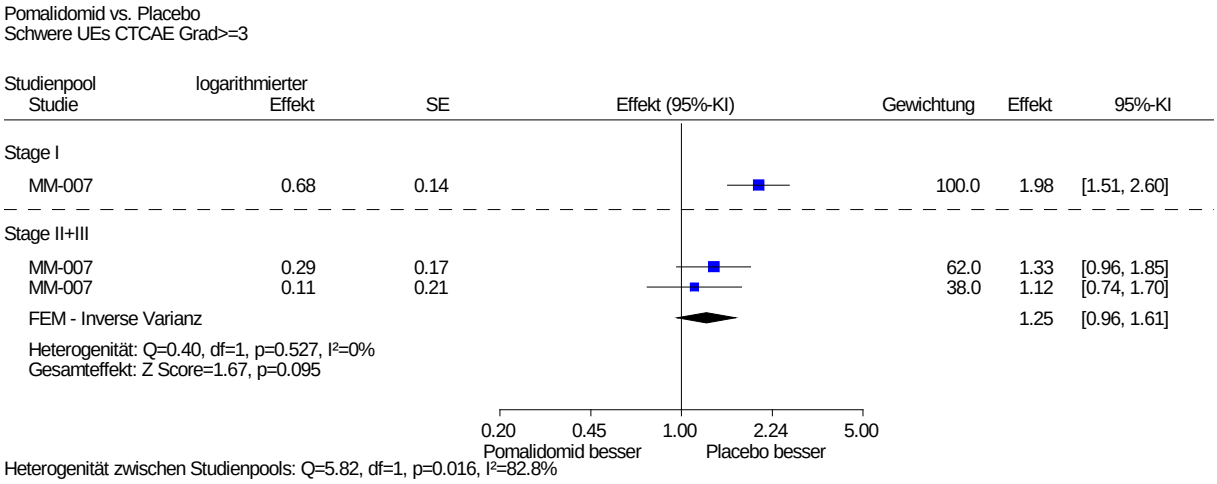

Figure 15: Forest Plot for aggregated subgroups with homogeneous effects (ISS stage I vs. ISS stages II and III) study MM-007 (data cut-off 2: 15 September 2018)