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Elotuzumab (multiple myeloma) –

Addendum to Commission A19-80[1]

Addendum

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[1] Translation of addendum A20-12 *Elotuzumab (multiples Myelom) – Addendum zum Auftrag A19-80* (Version 1.0; Status: 13 March 2020). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PT	Preferred Term
SAE	serious adverse event
SOC	System Organ Class

1 Background

On 10 February 2020, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A19-80 (Elotuzumab – Benefit assessment according to §35a Social Code Book V) [1].

In its dossier [2], the pharmaceutical company (hereinafter referred to as "the company") presented the randomized controlled trial (RCT) ELOQUENT-3 for the benefit assessment of elotuzumab in combination with pomalidomide and dexamethasone in patients with relapsed and refractory multiple myeloma who have received at least 2 prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy. This study was included in the benefit assessment [1].

Various relevant data on adverse events (AEs) were not available in the company's dossier, which made a choice of specific AEs impossible in the dossier assessment. With its comments [3], the company presented further analyses on AEs.

The G-BA's commission comprised the following assessments:

- assessment of the event time analyses on AEs at System Organ Class (SOC) and Preferred Term (PT) level
- assessment of the Kaplan-Meier curves on AEs provided by the company with the written comments
- assessment of the patient numbers with severe AEs of Common Terminology Criteria for Adverse Events (CTCAE) grade 5 on the basis of the data subsequently submitted in the written comments

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

The ELOQUENT-3 study, which compared elotuzumab + pomalidomide + dexamethasone with pomalidomide + dexamethasone was included in the dossier assessment. The following relevant information on AEs was not available:

- In its dossier for the benefit assessment of elotuzumab [2], the company had only presented the proportions of common AEs, serious AEs (SAEs), severe AEs (CTCAE grade 3–4), and discontinuations due to AEs at SOC and PT level. No choice of specific AEs was possible on the basis of these proportions, as there were relevant differences in the observation periods for AEs in the ELOQUENT-3 study. With its written comments, the company subsequently submitted the necessary event time analyses on AEs at SOC and PT level.
- The company had not presented any Kaplan-Meier curves on the AE outcomes with its dossier [2]. The section on risk of bias in the benefit assessment [1] addressed the fact that Kaplan-Meier curves are required for a more detailed assessment of the data situation. These were subsequently submitted with the company's written comments.
- The dossier did not contain any analyses on severe AEs of CTCAE grades 3–5 (corresponding to CTCAE grade ≥ 3), but only on the severity grades 3–4. In addition, there was no information on CTCAE grade 5 AEs (fatal AEs) available for the relevant data cut-off. With its written comments, the company subsequently submitted the overall rates on CTCAE grade 5 AEs for the relevant data cut-off from 29 November 2018.

The assessment of the data on specific AEs subsequently submitted can be found in Section 2.1. The assessment of the data on the overall AE rates subsequently submitted can be found in Section 2.2.

2.1 Specific adverse events

Risk of bias

Analogous to the results of the other AE outcomes in the dossier assessment [1], the risk of bias of the results on specific AEs was rated as high due to potentially informative censoring and lack of blinding in subjective recording of outcomes (only for non-serious/non-severe AEs). Hence, no more than hints of greater or lesser harm can be derived for these outcomes.

Results

Table 1 shows the results on specific AEs in the comparison of elotuzumab + pomalidomide + dexamethasone with pomalidomide + dexamethasone chosen on the basis of the event time analyses subsequently submitted. Kaplan-Meier curves on the specific AEs in the total population or separated by subgroups are not available. The Kaplan-Meier curves on the overall AE rates subsequently submitted by the company can be found in Appendix A.

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

Study Outcome category Outcome	Elotuzumab + pomalidomide + dexamethasone		Pomalidomide + dexamethasone		Elotuzumab + pomalidomide + dexamethasone vs. pomalidomide + 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]
ELOQUENT-3					
Side effects[b]					
Neutropenia (CTCAE grade 3–4)	60	NA 8 (13.3)	55	NA 16 (29.1)	0.41 [0.17; 0.97]; 0.033
Anaemia (CTCAE grade 3–4)	60	NA 6 (10.0)	55	NA 12 (21.8)	0.37 [0.14; 0.98]; 0.038

a. Effect estimation RR and 95% CI from Cox proportional hazards model, stratified by disease status at baseline (I–II vs. III) and number of prior therapies (2–3 vs. ≥ 4); p-value from stratified log-rank test.
b. Recording until 60 days after end of treatment.

CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NA: not achieved; PT: Preferred Term; RCT: randomized controlled trial; vs.: versus

A statistically significant difference in favour of elotuzumab + pomalidomide + dexamethasone was shown for each of the specific AEs "anaemia" and "neutropenia". This resulted in a hint of lesser harm from elotuzumab + pomalidomide + dexamethasone versus the appropriate comparator therapy (ACT) for each of these outcomes. It should be noted that both anaemia and neutropenia are events that can be allocated also to the underlying disease of multiple myeloma.

Subgroups and other effect modifiers

There are no subgroup analyses on the specific AEs.

2.2 Overall adverse event rates

Kaplan-Meier curves on the overall adverse event rates do not change the assessment of the risk of bias

As described in the dossier assessment [1], the risk of bias for the outcomes "SAEs", "severe AEs" (CTCAE grade 3–4) and "discontinuation due to AEs" (≥ 1 drug component) is rated as high. This assessment is not changed by the Kaplan-Meier curves subsequently submitted by the company (see Appendix A). The Kaplan-Meier curves present the occurrence of events over time. Based on the available figures, potentially informative censoring can still not be excluded, as a relevant extent of censorings occurred already at early time points and in the further course of the study.

Still no event time analyses on severe adverse events of CTCAE grade ≥ 3

There are still no event time analyses on severe AEs of CTCAE grades 3–5 (CTCAE grade ≥ 3). The proportions of CTCAE grade 5 AEs subsequently submitted by the company (elotuzumab + pomalidomide + dexamethasone: 7 [11.7%]; pomalidomide + dexamethasone: 9 [16.4%]) do not provide any further information for the interpretation of the results on severe AEs, as there is no information on how many of these patients already had severe AEs with CTCAE grade 3–4 before.

2.3 Extent and probability of added benefit

Table 2 shows probability and extent of the added benefit for the specific AEs subsequently submitted.

Table 2: Extent of added benefit at outcome level: elotuzumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone

Outcome category **Outcome**	**Elotuzumab + pomalidomide + dexamethasone** **vs.** **pomalidomide + dexamethasone** **Quantile of the time to event (months);** **p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
Specific AEs		
Anaemia (PT, severe AEs with CTCAE grade 3–4)	NA vs. NA HR: 0.41 [0.17, 0.97] p = 0.033 probability: “hint”	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ lesser harm, extent: “minor”
Neutropenia (PT, severe AEs with CTCAE grade 3–4)	NA vs. NA HR: 0.37 [0.14, 0.98] p = 0.038 probability: “hint”	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ lesser harm, extent: “minor”

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).

AE: adverse event; CI_u: upper limit of the confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; PT: Preferred Term; vs.: versus

2.3.1 Overall conclusion on added benefit

Table 3 summarizes the results of the dossier assessment [1] and of the present addendum that are included in the overall conclusion on the extent of added benefit.

Table 3: Positive and negative effects from the assessment of elotuzumab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone

Positive effects	**Negative effects**
Mortality ▪ Overall survival indication of an added benefit – extent: "minor"	-
Serious/severe side effects ▪ AEs (CTCAE grade 3–4) ▫ Number of prior lines of treatment: 2–3 hint of lesser harm – extent: "major" ▫ **Specific AEs:** - **Anaemia and neutropenia: in each case hint of lesser harm – extent: "minor"**	
The company's dossier did not contain any data on health-related quality of life.	
Results printed in **bold** result from the analyses subsequently submitted by the company with the written comments. AE: adverse event; CTCAE: Common Terminology Criteria of Adverse Events	

The analyses subsequently submitted with the comments resulted in further positive effects of elotuzumab in the specific AEs "anaemia" and "neutropenia" (each with CTCAE grade 3–4). No subgroup analyses are available for specific AEs. However, it is not assumed that, in the present situation, subgroup analyses of the specific AEs lead to results questioning the overall conclusion on the added benefit of elotuzumab + pomalidomide + dexamethasone. Overall, there is no change in the overall conclusion on the added benefit of elotuzumab + pomalidomide + dexamethasone versus the ACT.

2.4 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of elotuzumab from dossier assessment A19-80.

The following Table 4 shows the result of the benefit assessment of elotuzumab + pomalidomide + dexamethasone under consideration of dossier assessment A19-80 and the present addendum.

Table 4: Elotuzumab – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Elotuzumab in combination with pomalidomide and dexamethasone for the treatment of relapsed and refractory multiple myeloma in adult patients who have received at least 2 prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy[b]	▪ Bortezomib in combination with dexamethasone or ▪ lenalidomide in combination with dexamethasone or ▪ **pomalidomide 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	Indication of minor added 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**.
b. It is assumed that high-dose chemotherapy with stem cell transplantation is not an option for the patients at the time point of their current treatment.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The assessment described above deviates from that of the company, which derived an indication of considerable added benefit.

The G-BA decides on the added benefit.

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Elotuzumab (multiples Myelom): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A19-80 [online]. 20.12.2019 [Accessed: 11.01.2020]. (IQWiG-Berichte; Volume 857). URL: https://www.iqwig.de/download/A19-80_Elotuzumab_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

2. Bristol-Myers Squibb. Elotuzumab (EMPLICITI): Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 19.09.2019 [Accessed: 03.01.2020]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/496/#dossier.

3. Bristol-Myers Squibb. Stellungnahme vom 23.01.2020 zum IQWiG-Bericht Nr. 857: Elotuzumab (multiples Myelom); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A19-80. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/496/#beschluesse in the document "Zusammenfassende Dokumentation"].

Appendix A – Kaplan-Meier curves

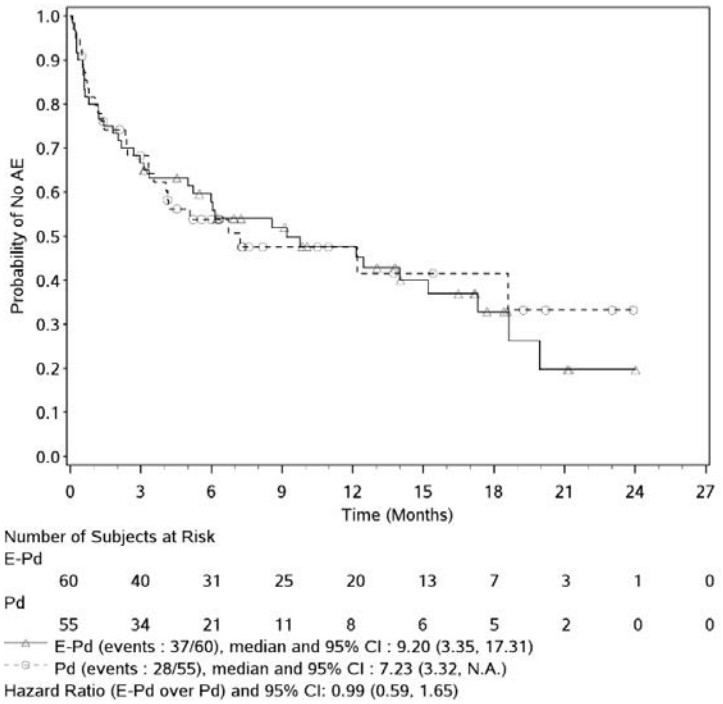

Figure 1: Kaplan-Meier curve on the outcome “SAEs”

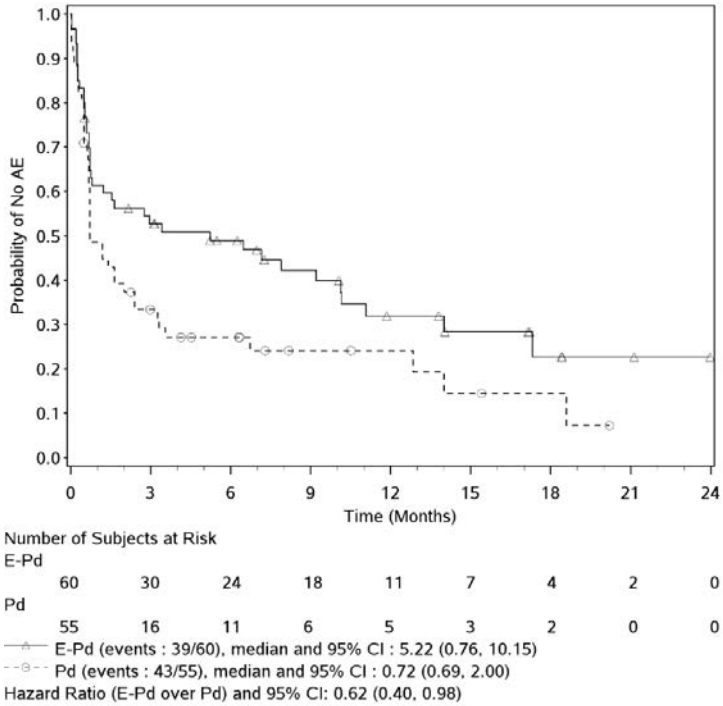

Figure 2: Kaplan-Meier curve on the outcome “severe AEs” (CTCAE grade 3–4)

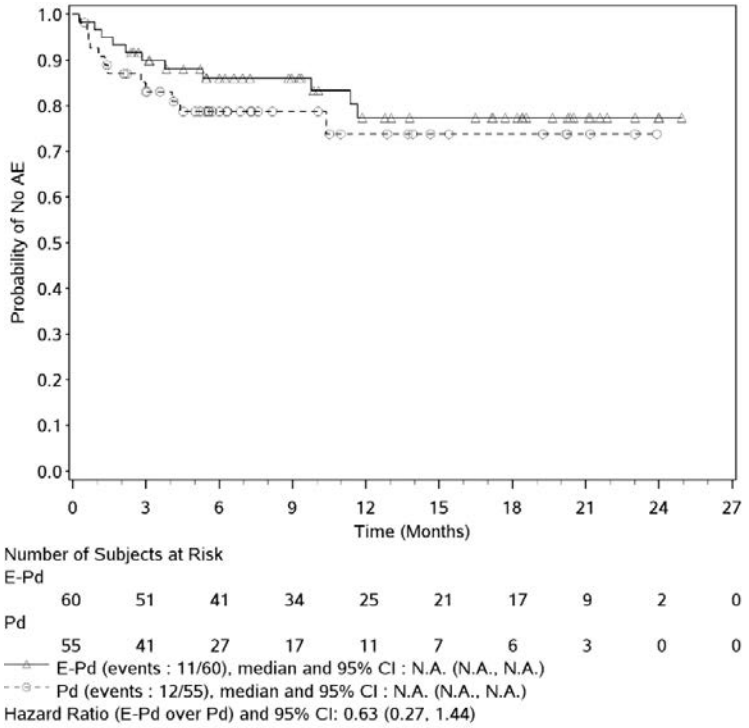

Figure 3: Kaplan-Meier curve on the outcome “discontinuation due to AEs”