IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Ribociclib (breast cancer) –

Addendum to Commission A17-45[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MID	minimally important difference
PT	Preferred Term
SAE	serious adverse event
SOC	System Organ Class
VAS	visual analogue scale

1 Background

On 22 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 A17-45 (Ribociclib – Benefit assessment according to §35a Social Code Book V) [1].

In its dossier [2], the pharmaceutical company (hereinafter referred to as "the company") presented results from the MONALEESA-2 study to prove the added benefit of ribociclib. This study was used for the dossier assessment [1]. Among other aspects, however, there were not enough usable data for the choice of specific adverse events (AEs).

With its written comments on the dossier assessment, the company submitted further data [3]. The G-BA commissioned IQWiG with the assessment of these data, particularly of the event time analyses on serious AEs (SAEs) and severe AEs at System Organ Class (SOC) level.

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 of the data on the MONALEESA-2 study subsequently submitted by the company

2.1 Specific adverse events

A choice of specific AEs for the MONALEESA-2 study was not possible in the dossier assessment because the company did not present complete event time analyses of all SOCs and Preferred Terms (PTs) for the patient-relevant outcomes "SAEs" and "severe AEs" (Common Terminology Criteria for Adverse Events [CTCAE] grade 3 or 4). The information presented in the dossier on the basis of the proportion of patients with events was not interpretable due to the differences in treatment durations and hence observation periods between the study arms.

With its written comments, the company subsequently submitted event time analyses at SOC level for SAEs and severe AEs (CTCAE grade 3 or 4). In conjunction with the data from the dossier, event time analyses at SOC level on AEs, SAEs and severe AEs were now available, as well as frequencies at SOC and PT level on AEs, SAEs, severe AEs, and discontinuation due to AEs.

Since event time analyses at PT level were still not available, the choice of specific AEs, severe AEs and SAEs was conducted based on the event time analyses at SOC level. Specific AEs were chosen using the events that occurred in the relevant study on the basis of frequency and differences between the treatment arms and under consideration of the patient relevance.

Table 1 shows the specific AEs for ribociclib + letrozole in comparison with placebo + letrozole. Kaplan-Meier curves on specific AEs that were presented by the company are shown in Appendix A.

Table 1: Results (side effects) – RCT, direct comparison: ribociclib + letrozole vs. placebo + letrozole

Study Outcome category Outcome	Ribociclib + letrozole		Placebo + letrozole		Ribociclib + letrozole vs. placebo + letrozole
	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
MONALEESA-2[a]					
Side effects[b]					
Specific AEs					
Eye disorders (AEs)	334	NA 90 (26.9)	330	NA 39 (11.8)	2.33 [1.60; 3.39]; < 0.001
Skin and subcutaneous tissue disorders (AEs)	334	4.7 [3.8; 7.4] 209 (62.6)	330	NA [17.2; NC] 126 (38.2)	2.11 [1.69; 2.64]; < 0.001
Blood and lymphatic system disorders (severe AEs)	334	13.1 [6.4; 20.7] 178 (53.3)	330	NA 9 (2.7)	26.89 [13.76; 52.56]; < 0.001
Gastrointestinal disorders (severe AEs)	334	NA 45 (13.5)	330	NA 11 (3.3)	4.02 [2.08; 7.77]; < 0.001
General disorders and administration site conditions (severe AEs)	334	NA [31.5; NC] 24 (7.2)	330	NA 7 (2.1)	3.34 [1.44; 7.77]; 0.003
Infections and infestations (severe AEs)	334	NA 26 (7.8)	330	NA 9 (2.7)	2.67 [1.25; 5.70]; 0.008
Investigations (severe AEs)	334	NA [26.7; NC] 127 (38.0)	330	NA 27 (8.2)	5.47 [3.61; 8.29]; < 0.001
Metabolism and nutrition disorders (severe AEs)	334	NA 36 (10.8)	330	NA 15 (4.5)	2.36 [1.29; 4.30]; 0.004

a: Data cut-off: 4 January 2017.
b: MedDRA version 19.0.
AE: adverse event; CI: confidence interval; HR: hazard ratio; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Statistically significant effects to the disadvantage of ribociclib + letrozole in comparison with placebo + letrozole were shown for all outcomes presented in Table 1.

Due to the large differences in observation periods between the treatment arms with possible informative censoring, there was principally a high risk of bias for the results on specific AEs. Hence at most hints, e.g. of an added benefit, can be derived. Despite the high risk of bias at outcome level, high certainty of results was assumed for the SOCs “blood and lymphatic system

disorders" (severe AEs) and "investigations" (severe AEs) due to the marked effect and the fact that the events occurred at early time points in the observation period (see Figure 3 and Figure 4). This resulted in indications of greater harm of ribociclib + letrozole in comparison with letrozole for the SOC "blood and lymphatic system disorders" (severe AEs) and the SOC "investigations" (severe AEs). For all other specific AEs presented in Table 1, there were hints of greater harm of ribociclib + letrozole in comparison with letrozole.

Hence the consideration of the specific AEs at SOC level confirmed the assessment of the side effects in the dossier assessment. The dossier assessment showed hints or indications of greater harm with at least considerable extent for the overall rates of the outcomes "SAEs", "severe AEs" and "discontinuation due to AEs" [1]. The present results on specific AEs did not change this assessment.

2.2 Health status (EQ-5D VAS)

The MONALEESA-2 study recorded health status with the visual analogue scale (VAS) of the European Quality of Life-5 Dimensions (EQ-5D) questionnaire. In its dossier, the company had presented responder analyses on the time to definitive deterioration by a minimally important difference (MID) of 10 [2]. Since the validation study for the EQ-5D VAS describes an MID of 7 to 10, considering only the MID of 10 was not meaningful [4], particularly as the responder analyses presented by the company in the dossier were specified post hoc. The dossier assessment used the analysis of the mean differences for the assessment of this outcome instead [1].

With its written comments on the dossier assessment, the company presented the responder analysis of the EQ-5D VAS with an MID of 7 [3]. The results are presented in Table 2 together with the analysis on the MID of 10, which was already provided in the dossier. The corresponding Kaplan-Meier curves are presented in Appendix B.

Table 2: Results (health status) – RCT, direct comparison: ribociclib + letrozole vs. placebo + letrozole

Study Outcome category Outcome	Ribociclib + letrozole N	Ribociclib + letrozole Median time to event in months [95% CI] Patients with event n (%)	Placebo + letrozole N	Placebo + letrozole Median time to event in months [95% CI] Patients with event n (%)	Ribociclib + letrozole vs. placebo + letrozole HR [95% CI]; p-value
MONALEESA-2[a]					
Morbidity – health status					
EQ-5D VAS – time to deterioration[b]					
MID 7	334	30.4 [27.7; NC] 83 (24.9)	334	28.0 [27.6; NC] 75 (22.5)	0.99 [0.72; 1.36]; 0.946
MID 10	334	NA [30.4; NC] 80 (24.0)	334	28.0 [27.6; NC] 72 (21.6)	0.99 [0.72; 1.37]; 0.960

a: Data cut-off: 4 January 2017.
b: Deterioration of the score was rated as event if this also applied to all subsequent values. Deaths were not recorded as event.
CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; MID: minimally important difference; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus

No statistically significant difference between the treatment arms was shown for the outcome "health status" both for an MID of 7 and for an MID of 10. This concurs with the results of the analysis of the mean differences presented in the dossier assessment [1]. As a result, there was still no hint of an added benefit of ribociclib + letrozole in comparison with letrozole for this outcome; an added benefit is therefore not proven.

2.3 Subgroup of hormonal therapy in the (neo)adjuvant setting

The dossier assessment did not consider the subgroup characteristic "hormonal therapy in the (neo)adjuvant setting" (nonsteroidal aromatase inhibitors and others versus tamoxifen versus none), which is relevant for the benefit assessment, because no subgroup analyses on the patient-relevant outcomes were available. In its written comments, the company subsequently submitted the p-values of the interaction tests for this subgroup characteristic [3]. There was no effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) for any of the outcomes. Hence, as in the dossier assessment, no subgroups were used for the assessment of the added benefit.

2.4 Summary

The data subsequently submitted by the company in the commenting procedure did not change the conclusion on the added benefit of ribociclib from dossier assessment A17-45.

The following Table 3 shows the result of the benefit assessment of ribociclib under consideration of dossier assessment A17-45 and the present addendum.

Table 3: Ribociclib – probability and extent of added benefit

Subindication	**ACT**[a]	**Probability and extent of added benefit**[b]
Initial endocrine therapy of HR-positive and HER2-negative advanced or metastatic breast cancer in postmenopausal women	Anastrozole or **letrozole** or, if applicable, tamoxifen if aromatase inhibitors are unsuitable	Indication 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**.
b: The relevant study compared ribociclib + letrozole with placebo + letrozole. Patients with stage IV disease (breast cancer with distant metastasis) and an ECOG PS of 0 or 1 were included. It remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2 or with other disease stages.
ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor

The G-BA decides on the added benefit.

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Ribociclib (Mammakarzinom): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A17-45 [online]. 13.12.2017 [Accessed: 04.01.2018]. (IQWiG-Berichte; Volume 567). URL: https://www.iqwig.de/download/A17-45_Ribociclib_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

2. Novartis Pharma. Ribociclib (Kisqali): Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 29.08.2017 [Accessed: 04.01.2018]. URL: https://www.g-ba.de/informationen/nutzenbewertung/311/.

3. Novartis. Stellungnahme zum IQWiG-Bericht Nr. 567: Ribociclib (Mammakarzinom); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A17-45 [Soon available under: https://www.g-ba.de/informationen/nutzenbewertung/311/ in the document "Zusammenfassende Dokumentation"].

4. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health and Quality of Life Outcomes 2007; 5: 70.

Appendix A – Kaplan-Meier curves on specific adverse events

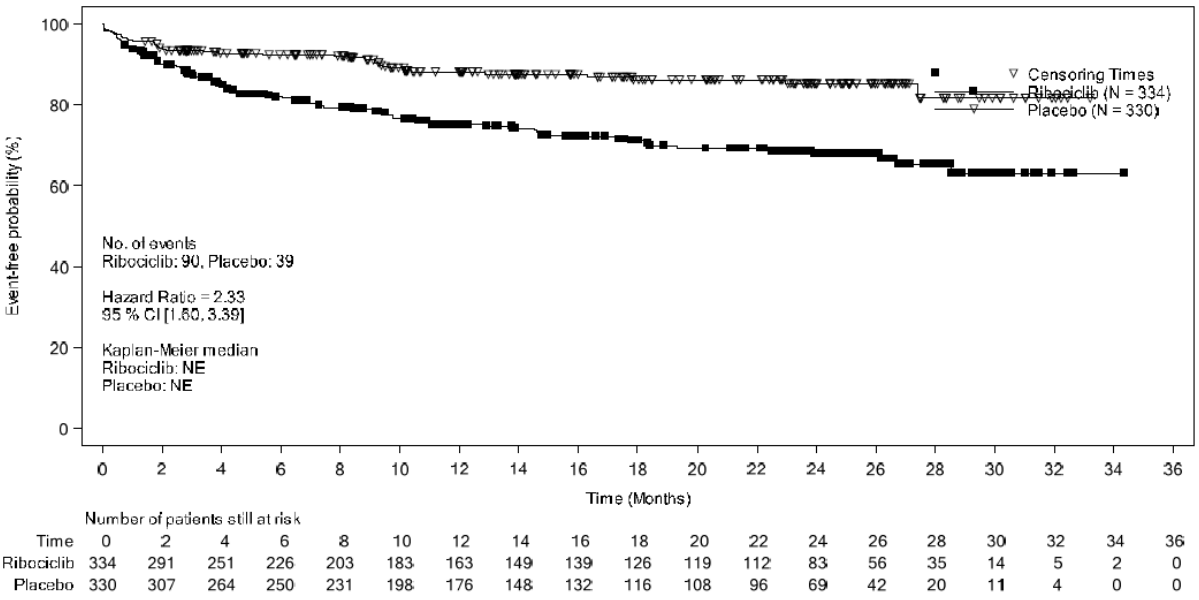

Figure 1: Kaplan-Meier curve on side effects; outcome “specific AEs” SOC “eye disorders” (AEs); study MONALEESA-2, data cut-off 4 January 2017

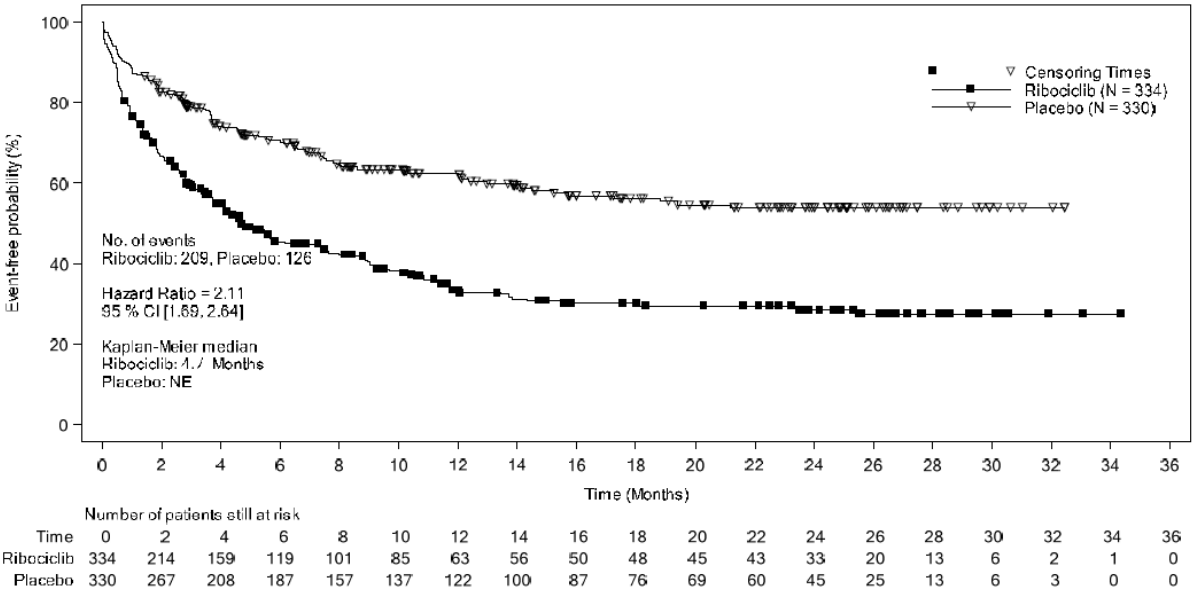

Figure 2: Kaplan-Meier curve on side effects; outcome “specific AEs” SOC “skin and subcutaneous tissue disorders” (AEs); study MONALEESA-2, data cut-off 4 January 2017

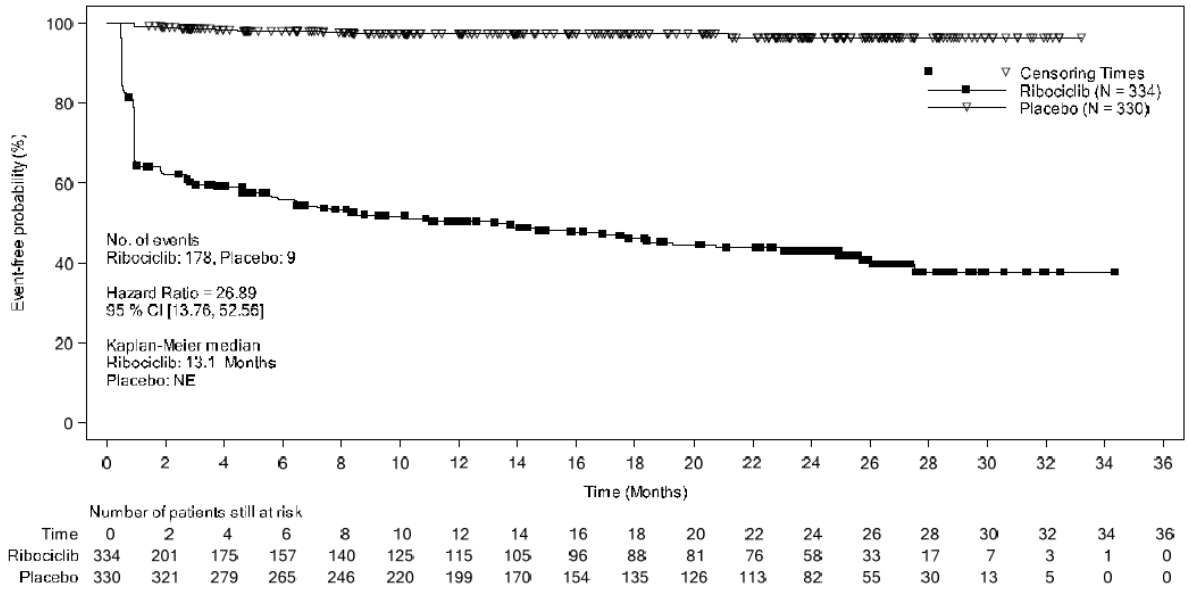

Figure 3: Kaplan-Meier curve on side effects; outcome "specific AEs" SOC "blood and lymphatic system disorders" (severe AEs); study MONALEESA-2, data cut-off 4 January 2017

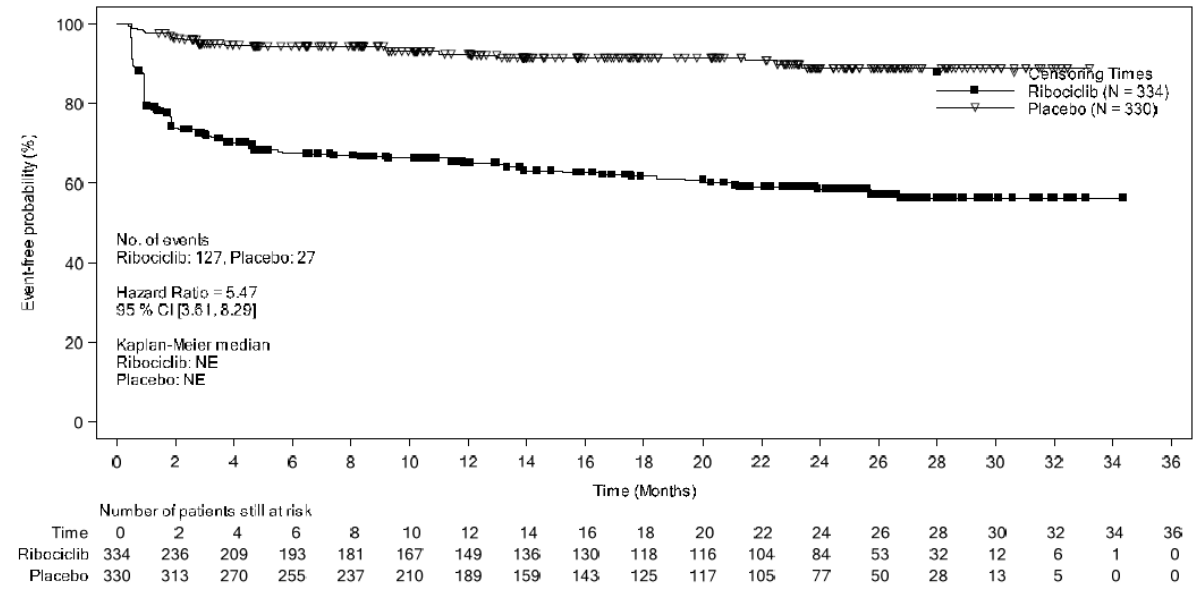

Figure 4: Kaplan-Meier curve on side effects; outcome "specific AEs" SOC "investigations" (severe AEs); study MONALEESA-2, data cut-off 4 January 2017

Appendix B – Kaplan-Meier curves on health status

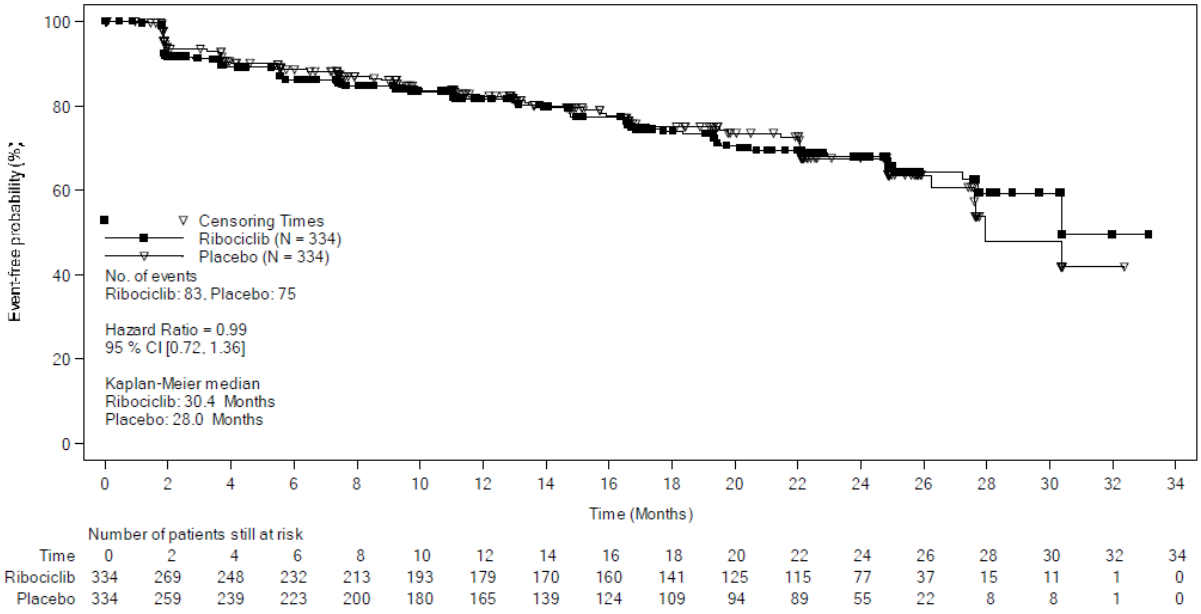

Figure 5: Kaplan-Meier curve on health status; outcome "EQ-5D VAS MID 7"; study MONALEESA-2, data cut-off 4 January 2017

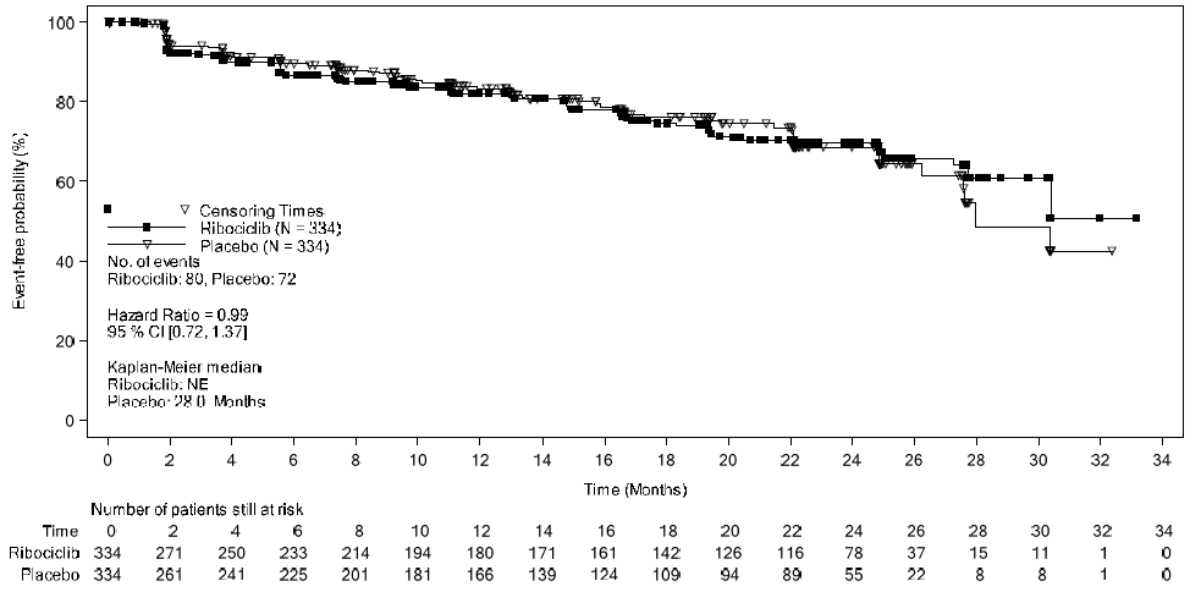

Figure 6: Kaplan-Meier curve on health status; outcome "EQ-5D VAS MID 10"; study MONALEESA-2, data cut-off 4 January 2017