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Ribociclib (breast cancer, combination with an aromatase inhibitor) – Addendum to Commission A20-21[1]

Addendum

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[1] Translation of addendum A20-57 *Ribociclib (Mammakarzinom, Kombination mit einem Aromatasehemmer) – Addendum zum Auftrag A20-21* (Version 1.0; Status: 30 July 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
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)
HER2	human epidermal growth factor receptor 2
HR	hormone receptor
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MMRM	mixed-effects model repeated measures
RCT	randomized controlled trial
SAE	serious adverse event
VAS	visual analogue scale

1 Background

On 6 July 2020, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A20-21 (Ribociclib – Benefit assessment according to §35a Social Code Book V) [1].

The randomized controlled trial (RCT) MONALEESA-2, which compared the combination of ribociclib + letrozole with placebo + letrozole, was included for the benefit assessment of ribociclib in combination with an aromatase inhibitor in postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer.

It was noted in dossier assessment A20-21 that there was no relevant analysis for the outcome "health status" (recorded with the European Quality of Life-5 Dimensions [EQ-5D] visual analogue scale [VAS]) and that the documentation on the methodological approach for the mixed-effects model repeated measures (MMRM) used was insufficient. The pharmaceutical company (hereinafter referred to as "the company") subsequently submitted this missing analysis with its comments [2]. Following the oral hearing, the company also subsequently submitted further information on the methodological approach and the patient numbers considered in the MMRM analyses [3,4]. Furthermore, the dossier assessment A20-21 noted the missing data on treatment duration and missing information for the determination of the outcome category for the outcome "discontinuation due to adverse events (AEs)", for which the company also subsequently submitted data with its comments.

The G-BA commissioned IQWiG with the assessment of these additional analyses and data submitted by the company under consideration of the information provided in the dossier [5].

- Study characteristics for the MONALEESA-2 study:
  - analysis of the time to discontinuation of the study medication including the corresponding Kaplan-Meier curves
- Results for the patient-relevant outcomes of the MONALEESA-2 study included in the assessment:
  - analyses regarding the change from baseline/analysis of the mean differences (MMRM analyses) for the outcome "health status" (EQ-5D VAS)
  - information on any AEs, serious AEs (SAEs) and severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade 3–4) leading to treatment discontinuation

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 RCT MONALEESA-2, which compared the combination of ribociclib + letrozole with placebo + letrozole, was included for the benefit assessment of ribociclib in combination with an aromatase inhibitor in postmenopausal women with HR-positive, HER2-negative locally advanced or metastatic breast cancer.

Analyses presented

Health status (EQ-5D VAS)

In the present addendum, the MMRM analysis was used for the outcome "health status" (EQ-5D VAS) for the consideration of the change from baseline. The responder analyses presented by the company in the dossier for the time to definitive deterioration were based on unvalidated response criteria and were therefore rated as not usable in dossier assessment A20-21 (see [1] for details).

MMRM analyses – documentation of the company on the methodological approach

The company stated in its documents subsequently submitted that its analyses for the MMRM model only included data from the period in which (at least) 50 patients per arm were still under treatment. These analyses were usable in the present data situation. In principle, however, analyses that take into account all data recorded are preferable.

Risk of bias

The assessment of the risk of bias across outcomes is in line with the assessment in dossier assessment A20-21. For the results presented for the EQ-5D VAS, the assessment on patient-reported outcomes in dossier assessment A20-21 applies. Consequently, a high risk of bias was assumed due to shortened observation periods for potentially informative reasons.

2.1 Study characteristics

Information on the course of the study

There was no information on treatment duration in dossier assessment A20-21 (data cut-off from 8 May 2019). The data subsequently submitted by the company on the analysis of the time to discontinuation of the study medication allow an estimation of the treatment duration and are presented in Table 1 (see Appendix A for the corresponding Kaplan-Meier curves).

Table 1: Information on the course of the study – RCT, direct comparison: ribociclib + letrozole vs. placebo + letrozole

Study **Duration of the study phase** **Outcome category**	**Ribociclib + letrozole** **N = 334**	**Placebo + letrozole** **N = 334**
MONALEESA-2 (data cut-off 8 May 2019)		
Treatment duration [months]		
Median [95% CI]	20.3 [16.7; 23.9]	13.7 [12.9; 16.0]
Mean (SD)	ND	ND

CI: confidence interval; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

2.2 Results (outcome level)

Table 2 shows the results of the comparison of ribociclib + letrozole with placebo + letrozole in postmenopausal patients with HR-positive, HER2-negative metastatic breast cancer for health status (EQ-5D VAS). Dossier assessment A20-21 considered the subgroup characteristic of age (< 65 years, ≥ 65 years), but results on subgroups for the outcome "health status" (EQ-5D VAS) are not available for this addendum.

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

Study **Outcome category** **Outcome**	**Ribociclib + letrozole**			**Placebo + letrozole**			**Ribociclib + letrozole vs. placebo + letrozole**
	N	**Values at baseline mean (SD)**	**Mean change in the course of the study mean [95% CI]**	**N**	**Values at baseline mean (SD)**	**Mean change in the course of the study mean [95% CI]**	**MD [95% CI][a]; p-value**
MONALEESA-2 (data cut-off 8 May 2019)							
Morbidity							
Health status							
EQ-5D VAS	306	ND	ND	304	ND	ND	−1.38 [−3.43; 0.67]; 0.187

a. Linear mixed-effects model repeated measures (MMRM) with change from baseline as a dependent variable, adjusted for values at baseline, stratified for the presence of liver and/or lung metastases. The resulting effect can be interpreted as a kind of average over the study period until the last time point at which at least 50 patients in each arm were still under treatment. A positive effect estimation indicates an advantage for ribociclib.

CI: confidence interval; EQ-5D European Quality of Life-5 Dimensions; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale; vs.: versus

Health status (EQ-5D VAS)

No statistically significant difference between the treatment arms was shown for the outcome "health status" recorded with the EQ-5D VAS. Hence, there was no hint of an added benefit of ribociclib + letrozole in comparison with letrozole; an added benefit is therefore not proven.

2.2.1 Outcome category for the outcome "discontinuation due to AEs"

For the outcome "discontinuation due to AEs", the data subsequently submitted by the company showed that, at the data cut-off from 8 May 2019, 67% (n = 44) of the AEs leading to discontinuation of the study medication in the ribociclib + letrozole arm, and 53% (n = 8) in the placebo + letrozole arm, were severe AEs (CTCAE grade 3–4). As was the case already in dossier assessment A20-21, the outcome "discontinuation due to AEs" was therefore allocated to the outcome category of serious/severe side effects.

2.3 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of ribociclib in combination with an aromatase inhibitor from dossier assessment A20-21.

The following Table 3 shows the result of the benefit assessment of ribociclib in combination with an aromatase inhibitor under consideration of dossier assessment A20-21 and the present addendum.

Table 3: Ribociclib in combination with an aromatase inhibitor – probability and extent of added benefit

Therapeutic indication[a]	**ACT**[b]	**Probability and extent of added benefit**
Initial endocrine therapy of HR-positive and HER2-negative advanced or metastatic breast cancer in postmenopausal women	Anastrozole or letrozole or fulvestrant or, if applicable, tamoxifen if aromatase inhibitors are unsuitable	Added benefit not proven[c]

a. It is assumed for the present therapeutic indication that endocrine therapy is indicated for the patients and that there is no indication for chemotherapy or (secondary) resection or radiotherapy with curative intent.
b. Presentation of the respective ACT specified by the G-BA.
c. Only patients with an ECOG PS of 0 or 1 were included in the MONALEESA-2 study. It remains unclear whether the observed results can be transferred to patients with an ECOG PS of ≥ 2. Almost all patients included in the study had stage IV disease (breast cancer with distant metastasis).

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, Kombination mit einem Aromatasehemmer): Nutzenbewertung gemäß § 35a SGB V (Ablauf Befristung); Dossierbewertung; Auftrag A20-21 [online]. 28.05.2020 [Accessed: 02.06.2020]. (IQWiG-Berichte; Volume 917). URL: https://www.iqwig.de/download/A20-21_Ribociclib_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

2. Novartis. Stellungnahme zum IQWiG-Bericht Nr. 917: Ribociclib (Mammakarzinom, Kombination mit einem Aromatasehemmer); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A20-21. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/526/#stellungnahmen in the document "Zusammenfassende Dokumentation"].

3. Gemeinsamer Bundesausschuss. Mündliche Anhörung gemäß § 35 a Abs. 3 Satz 2 SGB V; hier: Wirkstoff Ribociclib (D-517, D-518); stenografisches Wortprotokoll [online]. 06.07.2020 [Accessed: 20.07.2020]. URL: https://www.g-ba.de/downloads/91-1031-526/2020-07-06_Wortprotokoll_Ribociclib_D-517.pdf.

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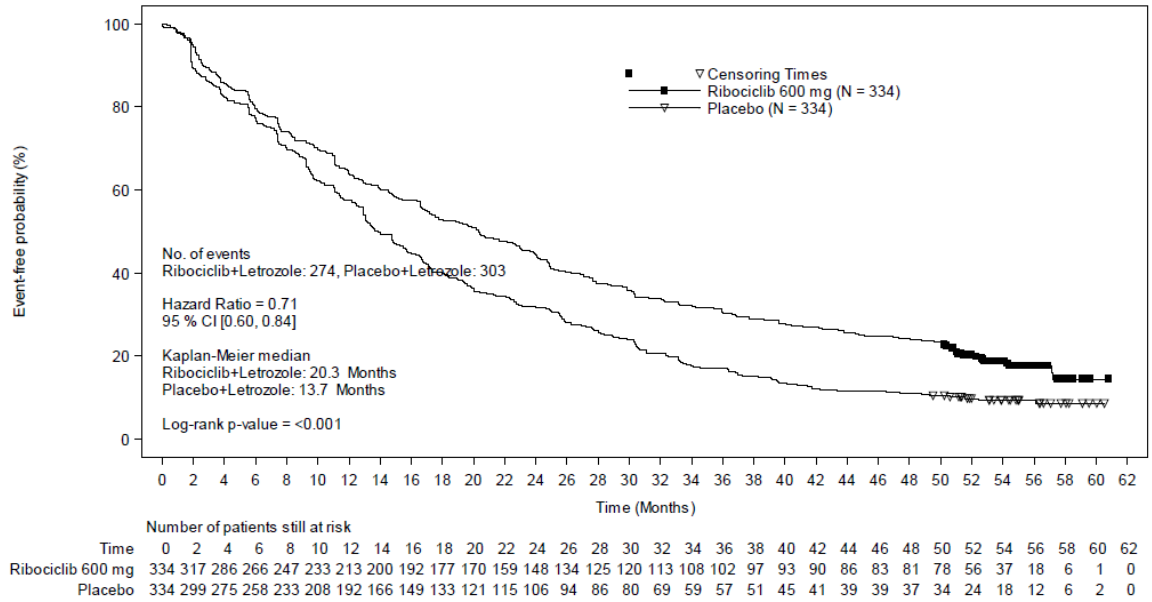
5. Novartis Pharma. Ribociclib (Kisqali): Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 28.02.2020 [Accessed: 19.06.2020]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/526/#dossier.

Appendix A – Information on the course of the study



Number of patients still at risk

Time	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	54	56	58	60	62
Ribociclib 600 mg	334	317	286	266	247	233	213	200	192	177	170	159	148	134	125	120	113	108	102	97	93	90	86	83	81	78	56	37	18	6	1	0
Placebo	334	299	275	258	233	208	192	166	149	133	121	115	106	94	86	80	69	59	57	51	45	41	39	39	37	34	24	18	12	6	2	0

Figure 1: Kaplan-Meier curves for the time to discontinuation of the study medication in MONALEESA-2