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Ribociclib (breast cancer; combination with fulvestrant) –

Addendum to Commission A19-06[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
BPI-SF	Brief Pain Inventory-Short Form
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)
MID	minimally important difference
MMRM	mixed-effects model repeated measures
PFS	progression-free survival
RCT	randomized controlled trial
SAE	serious adverse event
VAS	visual analogue scale

1 Background

On 27 May 2019, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A19-06 (Ribociclib – Benefit assessment according to §35a Social Code Book V) [1].

The randomized controlled trial (RCT) MONALEESA-3, which compared the combination of ribociclib + fulvestrant with placebo + fulvestrant, was included for the benefit assessment of ribociclib in combination with fulvestrant in postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor-2 (HER2)-negative locally advanced or metastatic breast cancer. Subpopulations from the study were used for research question A1 (initial endocrine therapy) and research question B1 (postmenopausal women who have received prior endocrine therapy).

After the oral hearing [2,3], the pharmaceutical company (hereinafter referred to as "the company") presented further analyses of subpopulations of the MONALEESA-3 study using new definitions of the patient groups.

The G-BA commissioned IQWiG with the assessment of the study results of the MONALEESA-3 study using the following definitions of the patient populations:

- Patient group A1:
  - patients who have never received endocrine therapy, and
  - patients who received a (neo)adjuvant endocrine therapy that must have been completed at least 12 months before diagnosis of recurrence, and
  - patients with recurrence during or ≤ 12 months after completion of (neo)adjuvant endocrine therapy
- Patient group B1:
  - patients with recurrence > 12 months after completion of (neo)adjuvant endocrine therapy and another progression after (first-line) endocrine therapy for the advanced stage, and
  - patients with initial diagnosis of metastatic breast cancer who progressed after first-line endocrine therapy for this stage

The definitions of the patient groups in the analyses subsequently submitted by the company after the hearing was in line with the definitions of the patient populations according to the commission by the G-BA.

The commission also comprised the assessment of the results of the responder analyses on the European Quality of Life-5 Dimensions (EQ-5D) visual analogue scale (VAS) (minimally important difference [MID] of 7 and 10 points) and the representation of the results on the outcomes "progression-free survival (PFS)" and "time to first subsequent chemotherapy".

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-3, which compared the combination of ribociclib + fulvestrant with placebo + fulvestrant, was included for the benefit assessment of ribociclib in combination with fulvestrant in postmenopausal women as initial endocrine therapy (research question A1) and in postmenopausal women who have received prior endocrine therapy (research question B1).

Operationalization of the subpopulations

For benefit assessment A19-06, the company's dossier contained subgroup analyses, in which it had conducted separate analyses of the study populations according to prior endocrine therapy:

- Patient group A1 of the dossier assessment (A19-06):
  - patients who have never received endocrine therapy, and
  - patients who received a (neo)adjuvant endocrine therapy that must have been completed at least 12 months before diagnosis of recurrence
- Patient group B1 of the dossier assessment (A19-06):
  - patients with recurrence during or ≤ 12 months after completion of (neo)adjuvant endocrine therapy
  - patients with recurrence > 12 months after completion of (neo)adjuvant endocrine therapy and another progression after (first-line) endocrine therapy for the advanced stage, and
  - patients with initial diagnosis of metastatic breast cancer who progressed after first-line endocrine therapy for this stage

This division was considered appropriate in dossier assessment A19-06 (see A19-06 for more details [1]).

In the oral hearing on ribociclib, the company was requested to subsequently submit analyses with the patient groups divided by their prior endocrine therapy for the advanced stage. In this division, patients with recurrence during or ≤ 12 months after completion of (neo)adjuvant endocrine therapy were not allocated to research question B1, but to research question A1. In accordance with the commission by the G-BA, the analyses of the present addendum were therefore based on the following divisions:

- Patient group A1, addendum A19-45 – postmenopausal women with initial endocrine therapy for the advanced stage:
  - patients who have never received endocrine therapy, and
  - patients who received a (neo)adjuvant endocrine therapy that must have been completed at least 12 months before diagnosis of recurrence, and

- patients with recurrence during or ≤ 12 months after completion of (neo)adjuvant endocrine therapy

- Patient group B1, addendum A19-45 – postmenopausal women who have received prior endocrine therapy for the advanced stage:
  - patients with recurrence > 12 months after completion of (neo)adjuvant endocrine therapy and another progression after (first-line) endocrine therapy for the advanced stage, and
  - patients with initial diagnosis of metastatic breast cancer who progressed after first-line endocrine therapy for this stage

Analyses presented

The analyses presented by the company on the new definitions of the patient populations contain results on all outcomes considered in the dossier assessment, except for the aspects described below. The included outcomes are described in detail in dossier assessment A19-06.

EQ-5D (VAS)

As was the case for the dossier assessment, the analyses for the new distribution of the patients also provided no usable results on health status recorded with the EQ-5D VAS. The analysis of the mean change compared with baseline had been planned in the MONALEESA-3 study. The company did not present such analyses also with the new analyses. Instead, as in the dossier, there were responder analyses on the time to deterioration on the response criteria ≥ 7 points and ≥ 10 points. These analyses were neither prespecified, nor has the validity of the used response criteria been shown in the sense of a minimally important difference (MID) (see A19-06). The responder analyses are presented as additional information in Appendix B.

Brief Pain Inventory – Short Form (BPI-SF)

As was the case for the dossier assessment, there were also no usable results on worst pain, pain intensity and pain interference recorded with the Brief Pain Inventory-Short Form (BPI-SF). Again, the company presented responder analyses on the time to deterioration for the item "worst pain" with a response criterion of ≥ 2 points. This analysis had not been prespecified in the MONALEESA-3 study. In addition, the company presented analyses as mean change compared with baseline from mixed-effects model repeated measures (MMRM) for the outcomes "worst pain", "pain intensity" and "pain interference", which were recorded with the BPI-SF scale. However, there was no corresponding documentation on the approach to the analyses presented. Hence, it cannot be inferred from the analyses whether and, if any, which of the results presented contain the adequate effect estimations.

Model of the event time analyses

It was not clear from the company's documents, which stratification factors were included in the model of the event time analyses. The stratification factors "presence of liver and/or lung metastases" and "prior endocrine therapy" had been prespecified for the MONALEESA-3

study. Since prior endocrine therapy was already reflected in the division of the populations for research questions A1 and B1 in dossier assessment A19-06, this stratification factor made no difference in the event time analyses presented in the dossier. According to the information provided by the company, stratification in the available analyses was either by presence of liver and/or lung metastases or by both stratification factors. This is marked correspondingly in the following result tables. It was assumed in the present situation, however, that this approach had no relevance for the assessment.

Further results

The results on the outcomes "PFS" and "time to first subsequent chemotherapy" are presented in Appendix A as additional information.

Risk of bias

The assessment of the risk of bias across outcomes and of the outcome-specific risk of bias was in line with dossier assessment A19-06 for the operationalizations of the subpopulations A1 and B1 used there. There was a high risk of bias both for the results on responder analyses of the EQ-5D presented as additional information and for the results of the other patient-reported outcomes.

2.1 Research question A1 – postmenopausal women with initial endocrine therapy for the advanced stage

The characteristics of the study and of the interventions of the MONALEESA-3 study can be found in dossier assessment A19-06. The company presented no patient characteristics for the newly defined subpopulation of women with initial endocrine therapy for the advanced stage with its analyses subsequently submitted. As was the case already in the dossier assessment, there was also no information on the course of the study for the subpopulations. The patient characteristics for the total population are presented in Appendix A (subpopulation A1 comprised 79% of the total population). Information on the course of the study for the total population of the MONALEESA-3 study can be found in Table 12 of dossier assessment A19-06.

2.1.1 Results

The results on the comparison of ribociclib + fulvestrant in postmenopausal women with HR-positive, HER2-negative locally advanced or metastatic breast cancer with initial endocrine therapy for the advanced stage are summarized in Table 1. The Kaplan-Meier curves on the presented event time analyses were not available in time for a comprehensive presentation. Kaplan-Meier curves on the outcomes "overall survival", "severe adverse events (AEs)" (Common Terminology Criteria for Adverse Events [CTCAE] grade 3–4), and blood and lymphatic system disorders (System Organ Class [SOC], CTCAE grade 3–4) can be found in Appendix C of the present addendum.

Table 1: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (postmenopausal women, initial endocrine therapy for the advanced stage)

Study **Outcome category**	**Ribociclib + fulvestrant**		**Placebo + fulvestrant**		**Ribociclib + fulvestrant vs. placebo + fulvestrant**
Outcome **Time point**	**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][a]; p-value[b]**
MONALEESA-3					
First data cut-off 3 November 2017					
Mortality					
Overall survival	375	NA 45 (12.0)	200	NA 37 (18.5)	0.66 [0.43; 1.02]; 0.061
Morbidity					
Symptoms					
EORTC QLQ-C30 (symptom scales)[c]					
Fatigue	375	22.4 [22.1; NC] 106 (28.3)	200	19.5 [17.7; NC] 56 (28.0)	0.96 [0.70; 1.34]; 0.829
Nausea/vomiting	375	NA 12 (3.2)	200	NA 4 (2.0)	1.35 [0.43; 4.23]; 0.605
Pain	375	NA [24.9; NC] 67 (17.9)	200	NA 29 (14.5)	1.16 [0.75; 1.80]; 0.513
Dyspnoea	375	NA 19 (5.1)	200	NA 12 (6.0)	0.73 [0.35; 1.52]; 0.398
Insomnia	375	NA 28 (7.5)	200	NA [24.9; NC] 12 (6.0)	1.16 [0.59; 2.28]; 0.676
Appetite loss	375	NA 23 (6.1)	200	NA 5 (2.5)	2.41 [0.91; 6.33]; 0.066
Constipation	375	NA 18 (4.8)	200	NA 6 (3.0)	1.59 [0.63; 4.01]; 0.323
Diarrhoea	375	NA 7 (1.9)	200	NA 0 (0)	–[d]; 0.065
Health status					
EQ-5D VAS	No usable data[e]				
Pain					
BPI-SF	No usable data[f]				

(continued)

Table 1: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (postmenopausal women, initial endocrine therapy for the advanced stage) (continued)

Study **Outcome category**	**Ribociclib + fulvestrant**		**Placebo + fulvestrant**		**Ribociclib + fulvestrant vs. placebo + fulvestrant**
Outcome **Time point**	**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][a]; p-value[b]**
Health-related quality of life					
EORTC QLQ-C30 (general health status and functional scales)[g]					
General health status	375	22.4 [22.1; NC] 107 (28.5)	200	19.4 [16.6; NC] 62 (31.0)	0.87 [0.63; 1.19]; 0.371
Physical functioning	375	22.1 [20.4; NC] 100 (26.7)	200	NA [19.4; NC] 47 (23.5)	1.07 [0.75; 1.51]; 0.724
Role functioning	375	NA [19.4; NC] 106 (28.3)	200	NA [22.3; NC] 42 (21.0)	1.33 [0.93; 1.91]; 0.116
Emotional functioning	375	22.3 [22.1; NC] 95 (25.3)	200	22.4 [19.4; NC] 49 (24.5)	0.96 [0.68; 1.36]; 0.838
Cognitive functioning	375	22.1 [19.4; NC] 111 (29.6)	200	22.4 [19.4; NC] 51 (25.5)	1.15 [0.83; 1.61]; 0.411
Social functioning	375	NA [22.4; NC] 89 (23.7)	200	22.9 [21.3; NC] 36 (18.0)	1.30 [0.88; 1.93]; 0.182
Side effects					
AEs (additional information)		0.3 [0.2; 0.3] 370 (98.9)		0.4 [0.3; 0.5] 192 (96.0)	
SAEs	374	NA 103 (27.5)	200	NA 34 (17.0)	1.61 [1.09; 2.38]; 0.015
Severe AEs (CTCAE grade 3–4)	374	1.9 [1.1; 1.9] 292 (78.1)	200	NA [20.2; NC] 60 (30.0)	4.49 [3.39; 5.95]; < 0.001
Discontinuation due to AEs[h]	374	NA [26.0; NC] 57 (15.2)	200	NA 13 (6.5)	2.33 [1.27; 4.26]; 0.005
Blood and lymphatic system disorders (SOC, CTCAE grade 3–4)	374	15.7 [9.3; NC] 171 (45.7)	200	NA 3 (1.5)	40.72 [13.00; 127.56]; < 0.001
Including: Neutropenia (PT, CTCAE grade 3-4)	374	19.3 [11.2; NC] 164 (43.9)	200	NA 0 (0)	–[d]; < 0.001

(continued)

Table 1: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (postmenopausal women, initial endocrine therapy for the advanced stage) (continued)

a: Cox proportional hazards model stratified by the presence of liver and/or lung metastases (outcome: overall survival), or stratified by the randomization strata presence of liver and/or lung metastases and prior endocrine therapy (all patient-reported outcomes and all outcomes of the category "side effects").
b: 2-sided log-rank test stratified by the presence of liver and/or lung metastases (outcome: overall survival), or stratified by the randomization strata presence of liver and/or lung metastases and prior endocrine therapy (all patient-reported outcomes and all outcomes of the category "side effects").
c: An increase in score by ≥ 10 points compared with baseline was considered definitive deterioration if this also applied to all subsequent values. Deaths were not recorded as events.
d: Effect estimation not meaningfully interpretable.
e: A supplementary presentation of the responder analyses on the response criteria of deterioration by ≥ 7 points and deterioration by ≥ 10 points can be found in Table 5 in Appendix A.
f: No information on the effect estimation.
g: A decrease in score by 10 points compared with baseline was considered definitive deterioration if this also applied to all subsequent values. Deaths were not recorded as events.
h: Defined as AEs that led to discontinuation of treatment with ribociclib or placebo; termination of fulvestrant treatment alone was not allowed in the framework of the study.
AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Patient-relevant outcomes with statistically significant differences in the MONALEESA-3 study

Mortality

Overall survival

The subpopulation considered here showed no statistically significant difference between the treatment groups for the outcome "overall survival". The total population of the MONALEESA-3 study showed a statistically significant difference in favour of ribociclib for this outcome (see Appendix A of dossier assessment A19-06). Due to the consistency of the direction of the effect and the position of the point estimations between the subpopulations A1 and B1 available here as well as of the total population of the MONALEESA-3 study, it is justified in the present data situation to transfer the results of the total population to the subpopulation when interpreting the results (similar data situation as in A19-06). Hence, an advantage of ribociclib was derived in research question A1 for the outcome "overall survival" in this data constellation.

Side effects

Serious adverse events and discontinuation due to adverse events

A statistically significant difference to the disadvantage of ribociclib was shown for each of the outcomes "serious adverse events (SAEs)" and "discontinuation due to adverse events (AEs)".

Severe adverse events (CTCAE grade 3–4) and blood and lymphatic system disorders (CTCAE grade 3–4)

A statistically significant difference to the disadvantage of ribociclib was shown for each of the outcomes "severe AEs" and "severe blood and lymphatic system disorders". Due to the size of the effect, there was a high certainty of results for this outcome despite high risk of bias.

Other outcomes

There were no statistically significant differences for all other outcomes of the categories "morbidity" and "health-related quality of life".

2.1.1.1 Subgroups and other effect modifiers

There were no data on subgroups of the newly defined subpopulation for research question A1.

2.1.2 Summarizing assessment of the results

In summary, the results of the MONALEESA-3 study led to both advantages and disadvantages of ribociclib + fulvestrant in comparison with placebo + fulvestrant regarding the following outcomes:

- Advantage in mortality (overall survival)
- Disadvantages in AE outcomes:
  - SAEs and discontinuation due to AEs
  - Severe AEs (CTCAE grade 3–4), including particularly blood and lymphatic system disorders (neutropenia): Due to the size of the effect, there was a high certainty of results for this outcome despite high risk of bias.

In the overall assessment, this resulted neither in an advantage nor in a disadvantage of ribociclib + fulvestrant in comparison with placebo + fulvestrant.

2.2 Research question B1 – postmenopausal women who have received prior endocrine therapy in the advanced stage

The characteristics of the study and of the interventions of the MONALEESA-3 study can be found in dossier assessment A19-06. With its analyses, the company presented no patient characteristics for the newly defined subpopulation of postmenopausal women who have received prior endocrine therapy for the advanced stage. As was the case already in the dossier assessment, there was also no information on the course of the study for the subpopulations.

2.2.1 Results

The results on the comparison of ribociclib + fulvestrant in postmenopausal women with HR-positive, HER2-negative locally advanced or metastatic breast cancer who have received prior endocrine therapy for the advanced stage are summarized in Table 2. The Kaplan-Meier curves on the presented event time analyses were not available in time for a comprehensive

presentation. Kaplan-Meier curves on the outcomes "overall survival", "severe AEs" (CTCAE grade 3–4), and blood and lymphatic system disorders (SOC, CTCAE grade 3–4) can be found in Appendix C of the present addendum.

Table 2: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (postmenopausal women who have received prior endocrine therapy for the advanced stage)

Study **Outcome category**	**Ribociclib + fulvestrant**		**Placebo + fulvestrant**		**Ribociclib + fulvestrant vs. placebo + fulvestrant**
Outcome **Time point**	**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][a]; p-value[b]**
MONALEESA-3					
First data cut-off 3 November 2017					
Mortality					
Overall survival	99	NA 24 (24.2)	38	NA [19.8; NC] 12 (31.6)	0.60 [0.30; 1.23]; 0.166
Morbidity					
Symptoms					
EORTC QLQ-C30 (symptom scales)[c]					
Fatigue	99	NA [14.8; NC] 27 (27.3)	38	NA [7.4; NC] 8 (21.1)	0.95 [0.43; 2.13]; 0.898
Nausea/vomiting	99	NA 1 (1.0)	38	NA 2 (5.3)	0.20 [0.02; 2.26]; 0.148
Pain	99	23.1 [22.0; NC] 20 (20.2)	38	16.7 [11.1; NC] 9 (23.7)	0.62 [0.28; 1.39]; 0.243
Dyspnoea	99	NA 3 (3.0)	38	22.1 [14.8; NC] 3 (7.9)	0.35 [0.07; 1.76]; 0.181
Insomnia	99	NA 8 (8.1)	38	NA 5 (13.2)	0.54 [0.17; 1.69]; 0.283
Appetite loss	99	NA 2 (2.0)	38	NA 0 (0)	–[d]; 0.388
Constipation	99	NA 3 (3.0)	38	NA 2 (5.3)	0.50 [0.08; 3.06]; 0.445
Diarrhoea	99	NA 0 (0)	38	NA 0 (0)	–
Health status					
EQ-5D VAS	No usable data[e]				
Pain					
BPI-SF	No usable data[f]				

(continued)

Table 2: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (postmenopausal women who have received prior endocrine therapy for the advanced stage) (continued)

Study **Outcome category**	**Ribociclib + fulvestrant**		**Placebo + fulvestrant**		**Ribociclib + fulvestrant vs. placebo + fulvestrant**
Outcome **Time point**	**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][a]; p-value[b]**
Health-related quality of life					
EORTC QLQ-C30 (general health status and functional scales)[g]					
General health status	99	NA [16.6; NC] 24 (24.2)	38	16.7 [11.8; NC] 12 (31.6)	0.58 [0.28; 1.20]; 0.142
Physical functioning	99	24.9 [16.6; NC] 26 (26.3)	38	14.8 [9.3; NC] 13 (34.2)	0.52 [0.26; 1.04]; 0.058
Role functioning	99	23.1 [16.5; NC] 26 (26.3)	38	16.7 [14.9; NC] 10 (26.3)	0.75 [0.35; 1.60]; 0.466
Emotional functioning	99	23.1 [17.4; NC] 24 (24.2)	38	19.5 [9.2; 22.6] 12 (31.6)	0.61 [0.30; 1.24]; 0.166
Cognitive functioning	99	22.0 [14.8; 23.1] 32 (32.3)	38	NA [14.8; NC] 6 (15.8)	1.42 [0.58; 3.51]; 0.449
Social functioning	99	24.9 [19.7; NC] 24 (24.2)	38	14.9 [11.2; NC] 12 (31.6)	0.51 [0.25; 1.06]; 0.070
Side effects					
AEs (additional information)	99	0.3 [0.1; 0.4] 99 (100)	38	0.5 [0.1; 1.0] 36 (94.7)	–
SAEs	99	NA [15.5; NC] 32 (32.3)	38	NA 6 (15.8)	1.94 [0.80; 4.69]; 0.137
Severe AEs (CTCAE grade 3–4)	99	1.8 [1.0; 3.8] 79 (79.8)	38	NA [9.6; NC] 11 (28.9)	3.69 [1.95; 7.01]; < 0.001
Discontinuation due to AEs[h]	99	NA 24 (24.2)	38	NA 2 (5.3)	4.58 [1.08; 19.48]; 0.024
Blood and lymphatic system disorders (SOC, CTCAE grade 3–4)	99	15.7 [7.4; NC] 44 (44.4)	38	NA 2 (5.3)	10.31 [2.49; 42.69] < 0.001
Including: Neutropenia (CTCAE grade 3–4)	99	NA [15.7; NC] 36 (36.4)	38	NA 0 (0)	–[d] < 0.001

(continued)

Table 2: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (postmenopausal women who have received prior endocrine therapy for the advanced stage) (continued)

a: Cox proportional hazards model stratified by the presence of liver and/or lung metastases (outcome: overall survival), or stratified by the randomization strata presence of liver and/or lung metastases and prior endocrine therapy (all patient-reported outcomes and all outcomes of the category "side effects").
b: 2-sided log-rank test stratified by the presence of liver and/or lung metastases (outcome: overall survival), or stratified by the randomization strata presence of liver and/or lung metastases and prior endocrine therapy (all patient-reported outcomes and all outcomes of the category "side effects").
c: An increase in score by ≥ 10 points compared with baseline was considered definitive deterioration if this also applied to all subsequent values.
d: Effect estimation not meaningfully interpretable.
e: A supplementary presentation of the responder analyses on the response criteria of deterioration by ≥ 7 points and deterioration by ≥ 10 points can be found in Table 6 in Appendix A.
f: No information on the effect estimation.
g: A decrease in score by 10 points compared with baseline was considered definitive deterioration if this also applied to all subsequent values.
h: Defined as AEs that led to discontinuation of treatment with ribociclib or placebo; termination of fulvestrant treatment alone was not allowed in the framework of the study.
AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Patient-relevant outcomes with statistically significant differences in the MONALEESA-3 study

Mortality

Overall survival

The subpopulation considered here showed no statistically significant difference between the treatment groups for the outcome "overall survival". The total population of the MONALEESA-3 study showed a statistically significant difference in favour of ribociclib for this outcome (see Appendix A of dossier assessment A19-06). The subpopulation B1 comprised only 19% of the study population. However, due to the consistency of the direction of the effect and the position of the point estimations between the subpopulations A1 and B1 available here as well as of the total population and further divisions of the study population of the MONALEESA-3 study (see also A19-06), it is justified in the present data situation to transfer the results of the total population to the subpopulation when interpreting the results. Hence, an advantage of ribociclib was derived in research question B1 for the outcome "overall survival" in this data constellation.

Side effects

Discontinuation due to adverse events

A statistically significant difference to the disadvantage of ribociclib was shown for the outcome “discontinuation due to AEs”.

Severe adverse events (CTCAE grade 3–4) and blood and lymphatic system disorders (CTCAE grade 3–4)

A statistically significant difference to the disadvantage of ribociclib was shown for each of the outcomes “severe AEs” and “severe blood and lymphatic system disorders”. Due to the size of the effect, there was a high certainty of results for this outcome despite high risk of bias.

Other outcomes

There were no statistically significant differences for all other outcomes of the categories “morbidity”, “health-related quality of life” and “side effects”.

2.2.1.1 Subgroups and other effect modifiers

There were no data on subgroups of the newly defined subpopulation for research question B1.

2.2.2 Summarizing assessment of the results

- Advantage in mortality (overall survival)
- Disadvantages in AE outcomes:
  - Discontinuation due to AEs
  - Severe AEs (CTCAE grade 3–4), including particularly blood and lymphatic system disorders (neutropenia): Due to the size of the effect, there was a high certainty of results for this outcome despite high risk of bias.

In the overall assessment, this resulted neither in an advantage nor in a disadvantage of ribociclib + fulvestrant in comparison with placebo + fulvestrant.

2.3 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 A19-06.

The following Table 3 shows the result of the benefit assessment of ribociclib under consideration of dossier assessment A19-06 and the present addendum.

Table 3: Ribociclib in combination with fulvestrant – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit[b]**
A1: postmenopausal women, initial endocrine therapy	Anastrozole or letrozole or fulvestrant or, if applicable, tamoxifen if aromatase inhibitors are unsuitable	▪ *Combination with fulvestrant:* added benefit not proven[c]
A2: pre- and perimenopausal women, initial endocrine therapy	Tamoxifen in combination with suppression of the ovarian function	▪ *Combination with fulvestrant:* added benefit not proven
B1: postmenopausal women who have received prior endocrine therapy	Another endocrine therapy in dependence on the pretreatment with: ▪ tamoxifen or ▪ anastrozole or ▪ fulvestrant; only for patients with recurrence or progression following anti-oestrogen therapy[d] or ▪ letrozole; only for patients with recurrence or progression following anti-oestrogen therapy or ▪ exemestane; only for patients with progression following anti-oestrogen therapy or ▪ everolimus in combination with exemestane; only for patients without symptomatic visceral metastases who have progressed after a non-steroidal aromatase inhibitor	▪ *Combination with fulvestrant:* added benefit not proven[e]
B2: pre- and perimenopausal women who have received prior endocrine therapy	Endocrine therapy specified by the physician under consideration of the respective approval Tamoxifen, letrozole, exemestane, megestrol acetate and medroxyprogesterone acetate are approved in the present therapeutic indication.	▪ *Combination with fulvestrant:* added benefit not proven

a: Presentation of the respective ACT specified by the G-BA.
b: It is assumed for the present therapeutic indications that (if applicable, another) endocrine therapy is indicated for the patients and that there is no indication for chemotherapy or (secondary) resection or radiotherapy with curative intent.
c: Overall, neither an advantage nor a disadvantage of ribociclib + fulvestrant resulted from the MONALEESA-3 study results also for the newly defined subpopulation of postmenopausal women with initial endocrine therapy for the advanced stage.
d: In therapeutic indication B1, the approval of fulvestrant provides for use of the drug only after prior anti-oestrogen therapy. In this respect, there is a discrepancy with the use of fulvestrant recommended in guidelines and established in health care, which do not focus exclusively on previous therapy with anti-oestrogens, but also on previous therapy with aromatase inhibitors. In this special therapeutic and health care situation, the G-BA sees a medical reason that, in the present case, exceptionally justifies considering fulvestrant as a comparison.
e: Overall, neither an advantage nor a disadvantage of ribociclib + fulvestrant resulted from the MONALEESA-3 study results also for the newly defined subpopulation of postmenopausal women who have received prior endocrine therapy for the advanced stage.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

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 A19-06 [online]. 11.04.2019 [Accessed: 24.04.2019]. (IQWiG-Berichte; Volume 752). URL: https://www.iqwig.de/download/A19-06_Ribociclib_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

2. Gemeinsamer Bundesausschuss. Mündliche Anhörung gemäß 5. Kapitel § 19 Abs. 2 Verfahrensordnung des Gemeinsamen Bundesausschusses; hier: Wirkstoff Ribociclib; stenographisches Wortprotokoll [online]. 27.05.2019 [Accessed: 05.06.2019]. URL: https://www.g-ba.de/downloads/91-1031-430/2019-05-27_Wortprotokoll_Ribociclib_D-430.pdf.

3. Novartis. Ribociclib (Kisqali): zusätzliche Analysen; Nachreichung von Auswertungen nach der mündlichen Anhörung zur Studie MONALEESA-3 [unpublished]. 2019.

Appendix A – Patient characteristics of the MONALEESA-3 study (total population)

Table 4: Characteristics of the study population – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (total population)

Study Characteristics Category	**Ribociclib + fulvestrant**	**Placebo + fulvestrant**
MONALEESA-3	N[a] = 484	N[a] = 242
Age [years], mean (SD)	63 (10)	63 (11)
Region, n (%)		
Asia		
Europe and Australia	347 (71.7)	173 (71.5)
North America	69 (14.3)	43 (17.8)
Asia	40 (8.3)	16 (6.6)
Latin America	6 (1.2)	3 (1.2)
Other	22 (4.5)	7 (2.9)
ECOG PS, n (%)		
0	310 (64.0)	158 (65.3)
1	173 (35.7)	83 (34.3)
Missing	1 (0.2)	1 (0.4)
Disease stage on study entry, n (%)		
II	2 (0.4)	0 (0)
III	4 (0.8)	2 (0.8)
IV	478 (98.8)	239 (98.8)
Missing	0 (0)	1 (0.4)
Disease-free interval, n (%)		
De novo	97 (20.0)	42 (17.4)
Not de novo	387 (80.0)	199 (82.2)
≤ 12 months	22 (4.5)	9 (3.7)
> 12 months	365 (75.4)	190 (78.5)
Missing	0 (0)	1 (0.4)
Previous drug treatment, n (%)		
Yes	375 (77.5)	193 (79.8)
No	109 (22.5)	48 (19.8)
Missing	0 (0)	1 (0.4)

(continued)

Table 4: Characteristics of the study population – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (total population) (continued)

Study Characteristics Category	**Ribociclib + fulvestrant**	**Placebo + fulvestrant**
MONALEESA-3	N[a] = 484	N[a] = 242
Type of most recent treatment, n (%)		
Chemotherapy	14 (2.9)	14 (5.8)
Endocrine therapy	206 (42.6)	100 (41.3)
Targeted therapy	3 (0.6)	1 (0.4)
Radiotherapy	133 (27.5)	74 (30.6)
Surgery (not biopsy)	65 (13.4)	37 (15.3)
Other	4 (0.8)	1 (0.4)
Setting of most recent treatment, n (%)[b]		
Adjuvant	200 (41.3)	111 (45.9)
Neoadjuvant	3 (0.6)	4 (1.7)
Therapeutic	82 (16.9)	34 (14.0)
Palliative	66 (13.6)	32 (13.2)
Not applicable	65 (13.4)	37 (15.3)
Location of metastases, n (%)[b]		
Bone	367 (75.8)	180 (74.4)
Bone only	103 (21.3)	51 (21.1)
Visceral	293 (60.5)	146 (60.3)
Lung or liver	242 (50.0)	121 (50.0)
Lung	146 (30.2)	72 (29.8)
Liver	134 (27.7)	63 (26.0)
CNS	6 (1.2)	2 (0.8)
Other	102 (21.1)	51 (21.1)
Lymph nodes	199 (41.1)	115 (47.5)
Soft tissue	23 (4.8)	14 (5.8)
Skin	20 (4.1)	8 (3.3)
Breast	4 (0.8)	1 (0.4)
None	2 (0.4)	0 (0)
Missing	0 (0)	1 (0.4)
Treatment discontinuation[c], n (%)	279 (57.6)	165 (68.2)
Study discontinuation, n (%)	ND	ND

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Multiple answers possible.
c: Discontinuation of entire study medication.
F: female; 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

Appendix B – Supplementary results on PFS, time to first chemotherapy and health status in the MONALEESA-3 study

B.1 – Research question A1

Table 5: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (postmenopausal women, initial endocrine therapy for the advanced stage)

Study Outcome category Outcome Time point	Ribociclib + fulvestrant N	Ribociclib + fulvestrant Median time to event in months [95% CI] Patients with event n (%)	Placebo + fulvestrant N	Placebo + fulvestrant Median time to event in months [95% CI] Patients with event n (%)	Ribociclib + fulvestrant vs. placebo + fulvestrant HR [95% CI][a]; p-value[b]
MONALEESA-3					
First data cut-off 3 November 2017					
Morbidity					
PFS[c]	375	20.6 [18.0; NC] 160 (42.7)	200	12.9 [11.0; NC] 124 (62.0)	0.61 [0.48; 0.77]; < 0.001
Time to first subsequent chemotherapy[d]	375	NA 112 (29.9[e])	200	26.6 [21.6; 26.6] 82 (41,e[d])	0.71 [0.54; 0.95]; 0.020
Health status (EQ-5D VAS)					
Deterioration ≥ 7 points[f]	375	22.2 [22.1; 25.8] 113 (30.1)	200	19.7 [19.4; NC] 58 (29.0)	0.98 [0.71; 1.35]; 0.901
Deterioration ≥ 10 points[f]	375	22.2 [22.1; 25.8] 105 (28.0)	200	19.7 [19.4; NC] 56 (28.0)	0.93 [0.67; 1.29]; 0.666

a: Cox proportional hazards model stratified by the presence of liver and/or lung metastases (outcome: PFS), or stratified by the randomization strata presence of liver and/or lung metastases and prior endocrine therapy (time to first chemotherapy, EQ-5D VAS).
b: 2-sided log-rank test stratified by the presence of liver and/or lung metastases (outcome: PFS), or stratified by the randomization strata presence of liver and/or lung metastases and prior endocrine therapy (time to first chemotherapy, EQ-5D VAS).
c: Defined as time to first documented progression (according to RECIST criteria [Version 1.1]) or death.
d: Defined as time to first subsequent chemotherapy or death.
e: Institute's calculation.
f: A decrease in score by ≥ 7 or ≥ 10 points compared with baseline was considered a clinically relevant deterioration if this also applied to all subsequent values.

AE: adverse event; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; NC: not calculable; PFS: progression-free survival; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumours; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

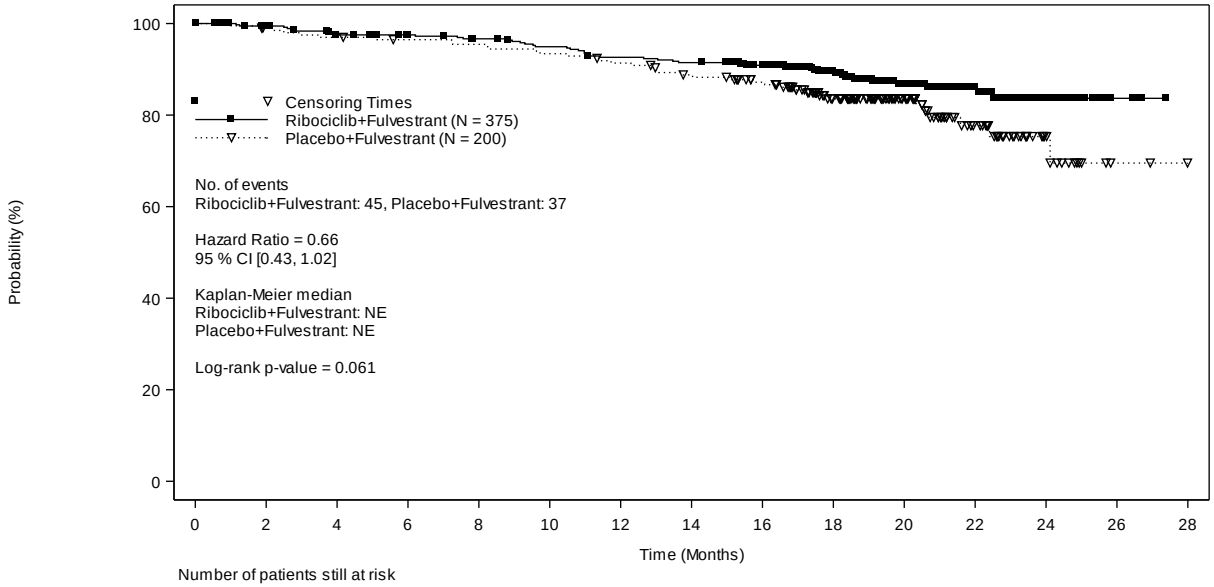
B.2 – Research question B1

Table 6: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (postmenopausal women who have received prior endocrine therapy for the advanced stage)

Study **Outcome category**	**Ribociclib + fulvestrant**		**Placebo + fulvestrant**		**Ribociclib + fulvestrant vs. placebo + fulvestrant**
Outcome **Time point**	**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][a]; p-value[b]**
MONALEESA-3					
First data cut-off 3 November 2017					
Morbidity					
PFS[c]	99	18.8 [12.5; NC] 47 (47.5)	38	11.4 [3.6; 16.3] 26 (68.4)	0.52 [0.32; 0.86]; 0.009
Time to first subsequent chemotherapy[d]	99	NA [16.2; NC] 42 (42.4[e])	38	16.6 [7.7; NC] 18 (47.4[e])	0.76 [0.43; 1.33]; 0.330
Health status (EQ-5D VAS)					
Deterioration ≥ 7 points[f]	99	19.0 [14.8; NC] 32 (32.3)	38	16.7 [9.3; NC] 11 (28.9)	0.92 [0.46; 1.86]; 0.825
Deterioration ≥ 10 points[f]	99	NA [14.8; NC] 30 (30.3)	38	16.7 [9.3; NC] 11 (28.9)	0.83 [0.41, 1.69] 0.614

a: Cox proportional hazards model stratified by the presence of liver and/or lung metastases (outcome: PFS), or stratified by the randomization strata presence of liver and/or lung metastases and prior endocrine therapy (time to first chemotherapy, EQ-5D VAS).
b: 2-sided log-rank test stratified by the presence of liver and/or lung metastases (outcome: PFS), or stratified by the randomization strata presence of liver and/or lung metastases and prior endocrine therapy (time to first chemotherapy, EQ-5D VAS).
c: Defined as time to first documented progression (according to RECIST criteria [Version 1.1]) or death.
d: Defined as time to first subsequent chemotherapy or death.
e: Institute's calculation.
f: A decrease in score by ≥ 7 or ≥ 10 points compared with baseline was considered a clinically relevant deterioration if this also applied to all subsequent values.
AE: adverse event; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; NC: not calculable; PFS: progression-free survival; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumours; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

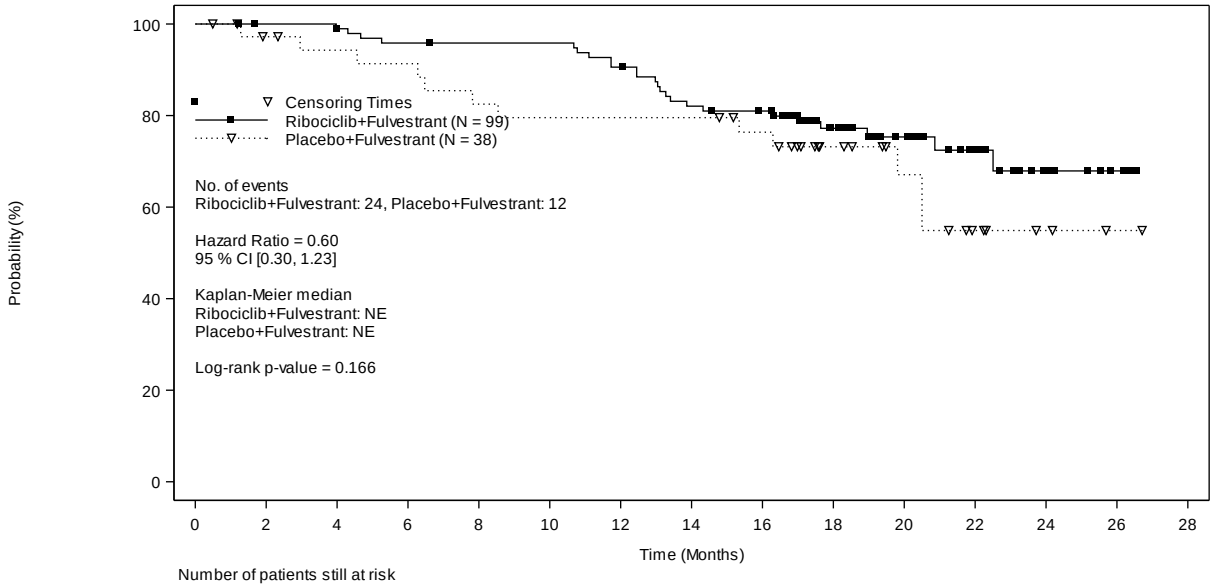
Appendix C – Graphic display of the event time analyses of the outcomes "overall survival", "severe AEs" (CTCAE grade 3–4) and "blood and lymphatic system disorders" (SOC, CTCAE grade 3–4) presented in the addendum



Number of patients still at risk

Time(months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28
Ribociclib+Fulvestrant	375	363	349	344	337	329	320	316	302	226	143	81	23	4	0
Placebo+Fulvestrant	200	196	192	189	187	183	178	170	159	119	77	39	14	2	0

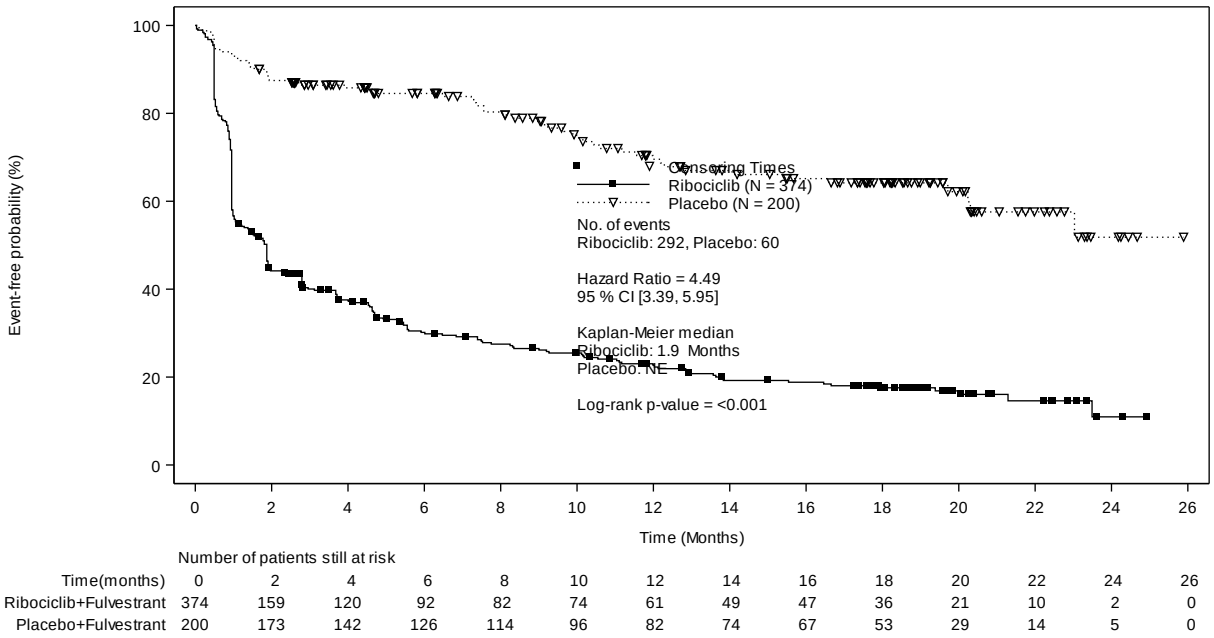
Figure 1: Kaplan-Meier curve on the outcome "overall survival" (subpopulation A1)



Number of patients still at risk

Time(months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28
Ribociclib+Fulvestrant	99	97	96	92	91	91	86	77	74	51	33	20	9	3	0
Placebo+Fulvestrant	38	34	32	31	28	27	27	27	24	16	11	6	3	1	0

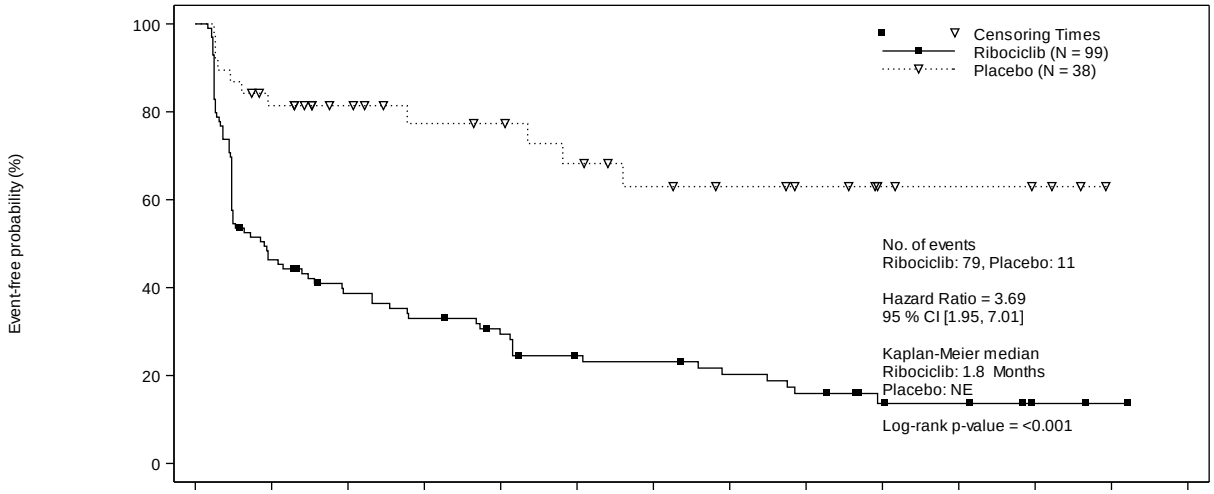
Figure 2: Kaplan-Meier curve on the outcome "overall survival" (subpopulation B1)



Number of patients still at risk

Time(months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26
Ribociclib+Fulvestrant	374	159	120	92	82	74	61	49	47	36	21	10	2	0
Placebo+Fulvestrant	200	173	142	126	114	96	82	74	67	53	29	14	5	0

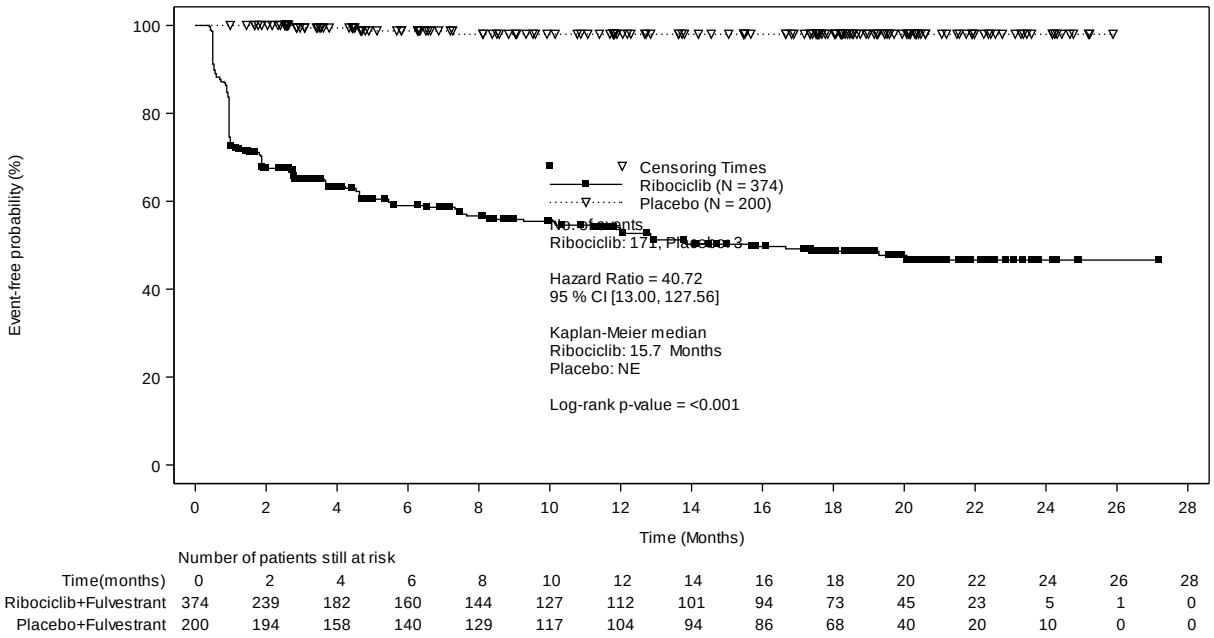
Figure 3: Kaplan-Meier curve on the outcome “severe AEs” (CTCAE grade 3–4), subpopulation A1



Number of patients still at risk

Time(months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26
Ribociclib+Fulvestrant	99	45	34	29	24	18	17	14	11	6	5	2	1	0
Placebo+Fulvestrant	38	29	23	19	18	15	12	10	8	5	4	3	0	0

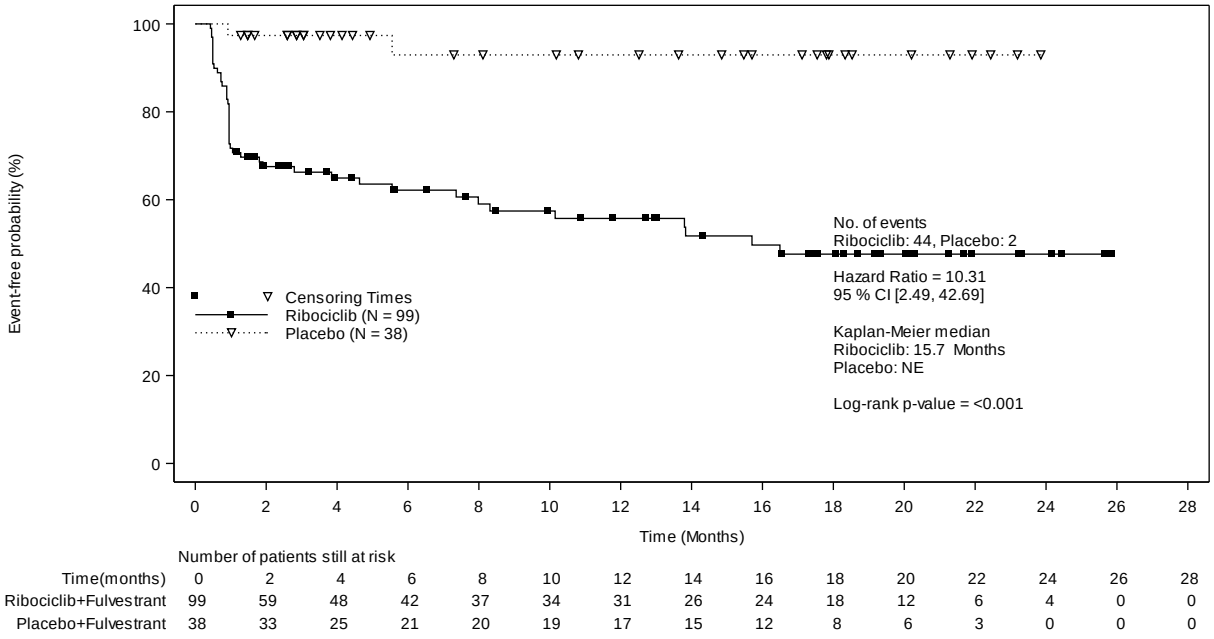
Figure 4: Kaplan-Meier curve on the outcome “severe AEs” (CTCAE grade 3–4), subpopulation B1



Number of patients still at risk

Time(months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28
Ribociclib+Fulvestrant	374	239	182	160	144	127	112	101	94	73	45	23	5	1	0
Placebo+Fulvestrant	200	194	158	140	129	117	104	94	86	68	40	20	10	0	0

Figure 5: Kaplan-Meier curve on the outcome “blood and lymphatic system disorders” (SOC, CTCAE grade 3–4), subpopulation A1



Number of patients still at risk

Time(months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28
Ribociclib+Fulvestrant	99	59	48	42	37	34	31	26	24	18	12	6	4	0	0
Placebo+Fulvestrant	38	33	25	21	20	19	17	15	12	8	6	3	0	0	0

Figure 6: Kaplan-Meier curve on the outcome “blood and lymphatic system disorders” (SOC, CTCAE grade 3–4), subpopulation B1