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Ribociclib (breast cancer; combination with an aromatase inhibitor) –

Addendum to Commission A19-06[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
EORTC QLQ-BR23	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer Module
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
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
NSAI	nonsteroidal aromatase inhibitor
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-7, which compared the combination of ribociclib + nonsteroidal aromatase inhibitor (NSAI) or ribociclib + tamoxifen with placebo + NSAI or placebo + tamoxifen, was included for the benefit assessment of ribociclib in combination with an aromatase inhibitor in pre- and perimenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor-2 (HER2)-negative locally advanced or metastatic breast cancer. From the MONALEESA-7 study, a subpopulation of patients with progression during or within 12 months after completion of (neo)adjuvant endocrine therapy is relevant for the comparison of ribociclib + NSAI versus placebo + NSAI (allocated to research question B2 in assessment A19-06) [1].

With its written comments on the dossier assessment [2,3] and after the oral hearing [4,5], the pharmaceutical company (hereinafter referred to as “the company”) submitted further analyses of a current data cut-off of the MONALEESA-7 study performed on 30 November 2018.

The G-BA commissioned IQWiG with the assessment of the data on subpopulation B2 at the current data cut-off (30 November 2018) including corresponding subgroup analyses. 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 presentation 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-7, which compared the combination of ribociclib + NSAI or ribociclib + tamoxifen with placebo + NSAI or placebo + tamoxifen in pre- and perimenopausal women with HR-positive, HER2-negative locally advanced or metastatic breast cancer, was included for the benefit assessment of ribociclib in combination with an aromatase inhibitor in pre- and perimenopausal women. From the MONALEESA-7 study, a subpopulation of patients with progression during or within 12 months after completion of (neo)adjuvant endocrine therapy was relevant for the comparison of ribociclib + NSAI versus placebo + NSAI (allocated to research question B2 in assessment A19-06) [1].

2.1 Description of the data situation

In its dossier, the company had used result of the MONALEESA-7 study from the first data cut-off from 3 November 2017. With its written comments, the company now presented results of a new data cut-off from 30 November 2018, which was the final data cut-off [2,4].

The analyses of the new data cut-off presented by the company contained results on all outcomes considered in the dossier assessment, both for the total population of the MONALEESA-7 study and for the subpopulation of interest, i.e. patients with progression during or within 12 months after completion of (neo)adjuvant endocrine therapy, for the comparison of ribociclib + NSAI versus placebo + NSAI. In addition, the company also presented subgroup analyses for this subpopulation after the oral hearing. The analyses of the subpopulation are relevant for the present research question.

2.2 Study characteristics

Information on the characteristics of the study and of the interventions of the MONALEESA-7 study as well as on the characteristics of the subpopulation can be found in the dossier assessment of ribociclib (A19-06 [1]).

Table 1 shows the mean/median treatment duration of the patients and the mean/median observation period for individual outcomes, in each case for the MONALEESA-7 sub-population of interest for the current data cut-off (for dossier assessment A19-06 only available for the total population). Information on the treatment duration and on the observation period of the outcome “overall survival” for this data cut-off was neither available for the subpopulation nor for the total population.

Table 1: Information on the course of the study – RCT, direct comparison: ribociclib + letrozole vs. placebo + letrozole (pre- and perimenopausal patients with progression during or within 12 months after completion of [neo]adjuvant endocrine therapy)

Study **Duration of the study phase** **Outcome category**	**Ribociclib + letrozole**	**Placebo + letrozole**
MONALEESA-7	N = 100	N = 105
Treatment duration [months]		
Median [min; max]	ND	ND
Mean (SD)	ND	ND
Observation period [months]		
Overall survival		
Median [min; max][a]	ND	ND
Mean (SD)	ND	ND
Symptoms/health-related quality of life		
EORTC QLQ-C30		
Median [min; max]	14.8 [−0.6; 38.7]	6.9 [−1.0; 38.9]
Mean (SD)	17.4 (12.0)	11.7 (11.5)
EORTC QLQ-BR23		
Median [min; max]	15.0 [−0.7; 38.7]	5.7 [−1.0; 35.9]
Mean (SD)	17.3 (12.0)	10.8 (10.8)
EQ-5D		
Median [min; max]	11.1 [−0.9; 38.7]	5.6 [−0.5; 35.9]
Mean (SD)	14.1 (12.2)	10.5 (11.3)
Side effects		
Median [min; max]	17.1 [1.0; 38.7]	8.3 [0.5; 40.0]
Mean (SD)	19.2 (11.9)	13.0 (11.4)

a: The median follow-up observation in the total population was 34.6 months.

EORTC QLQ-BR23: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer Module; 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; max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The median and the mean observation periods for the outcomes on symptoms, health-related quality of life and side effects showed clear differences between the study arms. This is due to the fact that patient-reported outcomes were only observed until progression, and adverse events (AEs) up to 30 days after the end of treatment.

2.3 Results

The included outcomes are described in detail in dossier assessment A19-06.

As was the case for the dossier assessment, the current data cut-off 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-7 study. The company did not present such analyses for the subpopulation of interest also for the new data cut-off. 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 an MID (see A19-06). The responder analyses are presented as additional information in Appendix A. The results on the outcomes "PFS" and "time to first subsequent chemotherapy" are also presented as additional information.

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. Due to the differences in observation periods with potentially informative censoring, 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.

The results of the new data cut-off from 30 November 2018 on the comparison of ribociclib + letrozole with placebo + letrozole in pre- and perimenopausal women with HR-positive, HER2-negative locally advanced or metastatic breast cancer who have progressed after endocrine therapy are summarized in Table 2. Kaplan-Meier curves on the presented event time analyses can be found in Appendix B of the present addendum.

Table 2: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: ribociclib + letrozole vs. placebo + letrozole (pre- and perimenopausal patients with progression during or within 12 months after completion of [neo]adjuvant endocrine therapy)

Study **Outcome category**	**Ribociclib + letrozole**		**Placebo + letrozole**		**Ribociclib + letrozole vs. placebo + letrozole**
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-7					
Second data cut-off 30 November 2018					
Mortality					
Overall survival	100	38.2 [38.2; NC] 35 (35.0)	105	36.7 [28.5; 40.9] 46 (43.8)	0.78 [0.50; 1.21]; 0.268
Morbidity					
Symptoms					
EORTC QLQ-C30 (symptom scales)[c]					
Fatigue	100	NA 20 (20.0)	105	33.1 [30.4; NC] 32 (30.5)	0.51 [0.29; 0.90]; 0.018
Nausea/vomiting	100	NA 7 (7.0)	105	NA 4 (3.8)	1.40 [0.40; 4.88]; 0.595
Pain	100	NA 16 (16.0)	105	33.1 [19.6; NC] 28 (26.7)	0.43 [0.23; 0.81]; 0.007
Dyspnoea	100	NA 5 (5.0)	105	NA 3 (2.9)	1.60 [0.38; 6.70]; 0.519
Insomnia	100	NA 11 (11.0)	105	NA 5 (4.8)	1.62 [0.56; 4.71]; 0.372
Appetite loss	100	NA 9 (9.0)	105	NA 6 (5.7)	1.28 [0.45; 3.63]; 0.639
Constipation	100	NA 8 (8.0)	105	NA 3 (2.9)	1.92 [0.50; 7.32] 0.334
Diarrhoea	100	NA 1 (1.0)	105	NA 1 (1.0)	0.95 [0.06; 15.30]; 0.972
EORTC QLQ-BR23 (symptom scales)[c]					
Side effects of systemic treatment	100	22.0 [14.8; 33.1] 47 (47.0)	105	16.6 [9.2; 27.6] 47 (44.8)	0.82 [0.54; 1.23]; 0.338
Symptoms in chest region	100	NA 14 (14.0)	105	33.2 [33.2; NC] 17 (16.2)	0.57 [0.28; 1.18]; 0.126

(continued)

Table 2: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: ribociclib + letrozole vs. placebo + letrozole (pre- and perimenopausal patients with progression during or within 12 months after completion of [neo]adjuvant endocrine therapy) (continued)

Study **Outcome category**	**Ribociclib + letrozole**		**Placebo + letrozole**		**Ribociclib + letrozole vs. placebo + letrozole**
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]**
EORTC QLQ-BR23 (symptom scales)[c]					
Symptoms in arm region	100	NA 17 (17.0)	105	NA 17 (16.2)	0.79 [0.40; 1.58]; 0.518
Upset by hair loss		No usable data[d]			
Health status					
EQ-5D VAS		No usable data[e]			
Health-related quality of life					
EORTC QLQ-C30 (general health status and functional scales)[f]					
General health status	100	33.1 [22.1; 35.9] 38 (38.0)	105	19.5 [14.7; 33.1] 38 (36.2)	0.74 [0.46; 1.19]; 0.203
Physical functioning	100	NA [33.2; NC] 22 (22.0)	105	NA [30.4; NC] 23 (21.9)	0.81 [0.45; 1.46]; 0.470
Role functioning	100	35.9 [27.6; NC] 29 (29.0)	105	27.9 [23.1; NC] 33 (31.4)	0.67 [0.40; 1.12]; 0.131
Emotional functioning	100	NA [24.9; NC] 32 (32.0)	105	27.7 [16.5; 33.1] 38 (36.2)	0.65 [0.40; 1.05]; 0.081
Cognitive functioning	100	NA [19.4; NC] 34 (34.0)	105	23.1 [11.3; 33.1] 40 (38.1)	0.61 [0.38; 0.97]; 0.040
Social functioning	100	35.9 [24.0; NC] 32 (32.0)	105	30.4 [22.3; NC] 30 (28.6)	0.76 [0.46; 1.27] 0.295
EORTC QLQ-BR23 (functional scales)[e]					
Body image	100	30.4 [19.4; 38.7] 40 (40.0)	105	27.5 [14.8; 35.9] 38 (36.2)	0.84 [0.53; 1.34]; 0.467
Sexual activity	100	NA [30.4; NC] 20 (20.0)	105	NA 20 (19.0)	0.92 [0.49; 1.71]; 0.793
Enjoyment of sex		No usable data[d]			
Future perspective	100	NA [33.1; NC] 16 (16.0)	105	24.8 [19.5; NC] 29 (27.6)	0.42 [0.23; 0.80]; 0.006

(continued)

Table 2: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: ribociclib + letrozole vs. placebo + letrozole (pre- and perimenopausal patients with progression during or within 12 months after completion of [neo]adjuvant endocrine therapy) (continued)

Study Outcome category Outcome Time point	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][a]; p-value[b]
Side effects					
AEs (additional information)	100	ND	105	ND	–
SAEs	100	36.4 [36.4; NC] 21 (21.0)		NA [27.33; NC] 19 (18.1)	0.89 [0.47; 1.67]; 0.709
Severe AEs (CTCAE grade 3–4)	100	1.0 [0.95; 1.97] 80 (80.0)		23.0 [14.39; NC] 40 (38.1)	3.23 [2.20; 4.75]; < 0.001
Discontinuation due to AEs[g]	100	NA 6 (6.0)	105	NA 4 (3.8)	1.16 [0.32; 4.18]; 0.822
Blood and lymphatic system disorders (SOC, CTCAE grade 3–4)	100	8.3 [1.0; NC] 56 (56.0)	105	NA 8 (7.6)	9.88 [4.69; 20.84]; < 0.001
Including: Neutropenia (PT, CTCAE grade 3–4)	100	11.1 [1.8; NC] 52 (52.0)	105	NA 5 (4.8)	13.50 [5.38; 33.91]; < 0.001

a: Cox proportional hazards model stratified by the presence of liver and/or lung metastases, prior chemotherapy in the advanced setting and endocrine combination partner (tamoxifen and goserelin vs. NSAI and goserelin), based on an extension of the Cox regression model with the corresponding subgroup variable and the interaction term treatment*subgroup variable.
b: 2-sided log-rank test stratified by the presence of liver and/or lung metastases, prior chemotherapy in the advanced setting and endocrine combination partner (tamoxifen and goserelin vs. NSAI and goserelin).
c: An increase in score by ≥ 10 points compared with baseline was considered a clinically relevant deterioration if this also applied to all subsequent values.
d: Unclear proportion of patients with missing values at baseline and in the course of the study; drastically decreasing proportion of patients in the analysis until the first documentation time (cycle 3).
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: A decrease in score by ≥ 10 points compared with baseline was considered a clinically relevant deterioration if this also applied to all subsequent values.
g: Defined as AEs that led to discontinuation of treatment with ribociclib or placebo; termination of letrozole treatment alone was not allowed in the framework of the study.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-BR23: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer Module; 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; ND: no data; NSAI: nonsteroidal aromatase inhibitor; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Based on the available data, indications, e.g. of an added benefit, can be determined for the outcomes "overall survival" and "discontinuation due to AEs". There was a high risk of bias of the results for the further outcomes; for the specific outcomes, however, the certainty of conclusions of the results was not always downgraded (see description of the results below and A19-06).

Mortality

Overall survival

The subpopulation considered here showed no statistically significant difference between the treatment groups for the outcome "overall survival".

It was checked in the present data situation whether the results for the outcome "overall survival" in the total population could be additionally used for the derivation of the added benefit. A statistically significant difference in favour of ribociclib was shown here (see Table 7 in Appendix A). However, an effect modification for this outcome was shown in the total population for the characteristic "ethnicity", according to which there was a statistically significant difference in favour of ribociclib only for patients of Asian ethnicity. There was no difference between the treatment groups for patients of other ethnicities (see Table 8, as well as Figure 2 and Figure 3 in Appendix A). For the subpopulation of interest, in contrast, there was no effect modification by ethnicity for the outcome "overall survival" ($p = 0.680$). For this reason, no advantage of ribociclib in comparison with the appropriate comparator therapy (ACT) can be derived for the total population, nor can a possible advantage be transferred to the subpopulation. For the subpopulation of interest, there was no effect modification by ethnicity for the outcome "overall survival".

This resulted in no hint of an added benefit of ribociclib + letrozole in comparison with letrozole. An added benefit for this outcome is therefore not proven.

Morbidity

Symptoms, recorded using the EORTC QLQ-C30 and the EORTC QLQ-BR23 (symptom scales)

Symptom outcomes were recorded with the symptom scales of the disease-specific instruments European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and EORTC Quality of Life Questionnaire-Breast Cancer Module (QLQ-BR23). In each case, the proportion of patients with definitive deterioration by ≥ 10 points was considered.

Fatigue and pain

As was the case in the first data cut-off from 3 November 2017, there was a statistically significant difference between the treatment groups in favour of ribociclib + letrozole for the outcome "pain". This resulted in a hint of an added benefit of ribociclib + letrozole in comparison with letrozole.

There was also a statistically significant difference in favour of ribociclib + letrozole for the outcome "fatigue". This effect was no more than marginal, however. As a result, there was no hint of an added benefit of ribociclib + letrozole versus letrozole for this outcome; an added benefit is not proven for this outcome.

Nausea/vomiting, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, side effects of systemic treatment, symptoms in the chest region, symptoms in the arm region, upset by hair loss

No statistically significant difference between the treatment groups was shown for each of the following outcomes: nausea/vomiting, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, side effects of systemic treatment, symptoms in the chest region and symptoms in the arm region. There were no usable data for the outcome "upset by hair loss". In each case, this resulted in no hint of an added benefit of ribociclib + letrozole in comparison with letrozole. An added benefit for these outcomes is therefore not proven.

Health status (EQ-5D VAS)

There were no usable data for the VAS of the EQ-5D questionnaire for the relevant subpopulation. A supplementary presentation of the results of the responder analyses on the response criteria of deterioration by ≥ 7 points or deterioration by ≥ 10 points can be found in Table 6 in Appendix A.

Health-related quality of life

EORTC QLQ-C30 and EORTC QLQ-BR23 (functional scales)

A statistically significant difference between the treatment groups was only shown for 2 outcomes in the functional scales of the EORTC questionnaires:

Cognitive functioning, future perspective

A statistically significant difference in favour of ribociclib + letrozole was shown for each of the outcomes "cognitive functioning" and "future perspective". In each case, this resulted in a hint of an added benefit of ribociclib + letrozole in comparison with letrozole.

Further functional scales

No statistically significant difference between the treatment groups was shown for each of the following outcomes: general health status, physical functioning, role functioning, emotional functioning, social functioning, body image, and sexual activity. There were no usable data for the outcome "enjoyment of sex". In each case, this resulted in no hint of an added benefit of ribociclib + letrozole in comparison with letrozole. An added benefit for these outcomes is therefore not proven.

Side effects

Serious adverse events

There was no statistically significant difference between the treatment groups for the outcome "serious AEs (SAEs)". This resulted in no hint of greater or lesser harm of ribociclib + letrozole in comparison with letrozole. An added benefit for this outcome is therefore not proven.

Severe adverse events (Common Terminology Criteria for Adverse Events [CTCAE] grade 3–4)

A statistically significant difference to the disadvantage of ribociclib + letrozole was shown for the outcome "severe AEs". Due to the size of the effect, there was an indication of greater harm of ribociclib + letrozole in comparison with letrozole despite the high risk of bias (a supplementary presentation of the Kaplan-Meier curve can be found in Appendix B).

Discontinuation due to adverse events

There was no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs". This resulted in no hint of an added benefit of ribociclib + letrozole in comparison with letrozole. An added benefit for this outcome is therefore not proven.

Blood and lymphatic system disorders (CTCAE grade 3–4)

A statistically significant difference to the disadvantage of ribociclib + letrozole was shown for the outcome "severe blood and lymphatic system disorders". Due to the size of the effect, there was an indication of greater harm of ribociclib + letrozole in comparison with letrozole despite the high risk of bias (a supplementary presentation of the Kaplan-Meier curve can be found in Appendix B).

2.3.1 Subgroups and other effect modifiers

After the oral hearing, the company presented subgroup analyses for the MONALEESA-7 subpopulation of interest. These comprised analyses on the potential effect modifiers of age, ethnicity, region and disease severity defined according to the dossier template. The company presented results of the respective tests for interaction (p-values). If there was a potential effect modification (p-value < 0.05), the company presented additional subgroup results.

The presented analyses produced no relevant subgroup results for the MONALEESA-7 subpopulation of interest.

2.4 Probability and extent of added benefit

The derivation of probability and extent of the added benefit per subpopulation is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [6].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.4.1 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 Section 2 (see Table 3).

Information on the determination of the outcome categories for the symptom outcomes can be found in dossier assessment A19-06.

Table 3: Extent of added benefit at outcome level: ribociclib + letrozole vs. placebo + letrozole (pre- and perimenopausal women with progression during or within 12 months after completion of [neo]adjuvant endocrine therapy)

Outcome category **Outcome**	**Ribociclib + letrozole vs. placebo + letrozole** **Median time to event (months)** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	38.2 vs. 36.7 HR: 0.78 [0.50; 1.21]; p = 0.268	Lesser benefit/added benefit not proven
Morbidity		
EORTC QLQ-C30 (symptom scales)		
Fatigue	NA vs. 33.1 HR: 0.51 [0.29; 0.90] p = 0.018	Outcome category non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[c]
Nausea/vomiting	NA vs. NA HR: 1.40 [0.40; 4.88] p = 0.595	Lesser benefit/added benefit not proven
Pain	NA vs. 33.1 HR: 0.43 [0.23; 0.81] p = 0.007 probability: “hint”	Outcome category non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ added benefit, extent: “minor”
Dyspnoea	NA vs. NA HR: 1.60 [0.38; 6.70] p = 0.519	Lesser benefit/added benefit not proven
Insomnia	NA vs. NA HR: 1.62 [0.56; 4.71] p = 0.372	Lesser benefit/added benefit not proven
Appetite loss	NA vs. NA HR: 1.28 [0.45; 3.63] p = 0.639	Lesser benefit/added benefit not proven
Constipation	NA vs. NA HR: 1.92 [0.50; 7.32] p = 0.334	Lesser benefit/added benefit not proven
Diarrhoea	NA vs. NA HR: 0.95 [0.06; 15.30] p = 0.972	Lesser benefit/added benefit not proven

(continued)

Table 3: Extent of added benefit at outcome level: ribociclib + letrozole vs. placebo + letrozole (pre- and perimenopausal women with progression during or within 12 months after completion of [neo]adjuvant endocrine therapy) (continued)

Outcome category **Outcome**	**Ribociclib + letrozole vs. placebo + letrozole** **Median time to event (months)** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
EORTC QLQ-BR23 (symptom scales)		
Side effects of systemic treatment	22.0 vs. 16.6 HR: 0.82 [0.54; 1.23] p = 0.338	Lesser benefit/added benefit not proven
Symptoms in chest region	NA vs. 33.2 HR: 0.57 [0.28; 1.18] p = 0.126	Lesser benefit/added benefit not proven
Symptoms in arm region	NA vs. NA HR: 0.79 [0.40; 1.58] p = 0.518	Lesser benefit/added benefit not proven
Upset by hair loss	No usable data available	
Health status		
EQ-5D VAS	No usable data available	
Health-related quality of life		
EORTC QLQ-C30 (functional scales)		
General health status	33.1 vs. 19.5 HR: 0.74 [0.46; 1.19] p = 0.203	Lesser benefit/added benefit not proven
Physical functioning	NA vs. NA HR: 0.81 [0.45; 1.46] p = 0.470	Lesser benefit/added benefit not proven
Role functioning	35.9 vs. 27.9 HR: 0.67 [0.40; 1.12] p = 0.131	Lesser benefit/added benefit not proven
Emotional functioning	NA vs. 27.7 HR: 0.65 [0.40; 1.05] p = 0.081	Lesser benefit/added benefit not proven
Cognitive functioning	NA vs. 23.1 HR: 0.61 [0.38; 0.97] p = 0.040 probability: “hint”	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: “minor”

(continued)

Table 3: Extent of added benefit at outcome level: ribociclib + letrozole vs. placebo + letrozole (pre- and perimenopausal women with progression during or within 12 months after completion of [neo]adjuvant endocrine therapy) (continued)

Outcome category **Outcome**	**Ribociclib + letrozole vs. placebo + letrozole** **Median time to event (months)** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Social functioning	35.9 vs. 30.4 HR: 0.76 [0.46; 1.27] p = 0.295	Lesser benefit/added benefit not proven
EORTC QLQ-BR23 (functional scales)		
Body image	30.4 vs. 27.5 HR: 0.84 [0.53; 1.34] p = 0.467	Lesser benefit/added benefit not proven
Sexual activity	NA vs. NA HR: 0.92 [0.49; 1.71] p = 0.793	Lesser benefit/added benefit not proven
Enjoyment of sex	No usable data available	
Future perspective	NA vs. 24.8 HR: 0.42 [0.23; 0.80] p = 0.006 probability: "hint"	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ added benefit, extent: "considerable"
Side effects		
SAEs	36.4 vs. NA HR: 0.89 [0.47; 1.67] p = 0.709	Greater/lesser harm not proven
Severe AEs (CTCAE grade 3–4)	1.0 vs. 23.0 HR: 3.23 [2.20; 4.75] HR: 0.31 [0.21; 0.45][d] p < 0.001 probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk ≥ 5% greater harm, extent: "major"
Discontinuation due to AEs	NA vs. NA HR: 1.16 [0.32; 4.18] p = 0.822	Greater/lesser harm not proven
Blood and lymphatic system disorders (SOC, CTCAE grade 3–4)	8.3 vs. NA HR: 9.88 [4.69; 20.84] HR: 0.10 [0.05; 0.21][d] p < 0.001 probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk ≥ 5% greater harm, extent: "major"

(continued)

Table 3: Extent of added benefit at outcome level: ribociclib + letrozole vs. placebo + letrozole (pre- and perimenopausal women with progression during or within 12 months after completion of [neo]adjuvant endocrine therapy) (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: The extent of the effect in this non-serious/non-severe outcome was no more than marginal. d: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit. AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-BR23: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer Module; 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; NA: not achieved; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

2.5 Overall conclusion on added benefit

Relevant data were available for the combination of ribociclib + aromatase inhibitor for pre- and perimenopausal patients with (neo)adjuvant tamoxifen pretreatment and with recurrence during or within 12 months after completion of (neo)adjuvant therapy. This subpopulation was allocated to research question B2 in the dossier assessment. No data were available from the MONALEESA-7 study for patients who, irrespective of (neo)adjuvant therapy, have already received endocrine therapy for their locally advanced or metastatic breast cancer.

Table 4 summarizes the results, under consideration of the results of the addendum, taken into account in the overall conclusion on the extent of added benefit.

Table 4: Positive and negative effects from the assessment of ribociclib + letrozole in comparison with letrozole (pre- and perimenopausal patients with progression during or within 12 months after completion of [neo]adjuvant endocrine therapy)

Positive effects	**Negative effects**
Hint of an added benefit – extent: "minor" (morbidity: pain)	Serious/severe side effects Overall rate of severe AEs (CTCAE grade 3–4): indication of greater harm – extent: "major" ▪ including in particular: SOC blood and lymphatic system disorders
Hint of an added benefit – extent: "minor" (health-related quality of life: cognitive functioning)	
Hint of an added benefit – extent: "considerable" (health-related quality of life: future perspective)	
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; SOC: System Organ Class	

As was the case already in the dossier assessment based on the data cut-off from 20 August 2017, there were both positive and negative effects of ribociclib versus the ACT from the current data cut-off.

Hints of an added benefit of ribociclib were shown for the symptom “pain” and for 2 of a total of 10 aspects of health-related quality of life (cognitive functioning and future perspective). The extents were minor to considerable. This was accompanied by an indication of greater harm of major extent in severe AEs, including blood and lymphatic system disorders in particular.

There were only hints for all effects in favour of ribociclib. In addition, there was no consistent picture of an advantage across several outcomes for health-related quality of life, but only for 2 of a total of 10 outcomes. This does not allow the derivation of an added benefit for health-related quality of life as a whole. One positive effect on symptom outcomes remains, which, however, is not sufficient in its certainty of conclusions and its extent to compensate for the observed disadvantage from severe side effects.

In summary, there is an indication of lesser benefit of ribociclib + letrozole versus letrozole for pre- and perimenopausal patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer and with recurrence during or within 12 months after completion of (neo)adjuvant therapy.

2.6 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 5 shows the result of the benefit assessment of ribociclib under consideration of dossier assessment A19-06 and the present addendum.

Table 5: Ribociclib in combination with an aromatase inhibitor – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit[b]**
A2: pre- and perimenopausal women, initial endocrine therapy	Tamoxifen in combination with suppression of the ovarian function	▪ *Combination with aromatase inhibitor:* 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[c] 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 aromatase inhibitor:* added benefit not proven
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 aromatase inhibitor:* indication of lesser benefit[d, e]

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: 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.
d: Only patients with an ECOG PS of 0 or 1 were included in the MONALEESA-7 study. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.
e: This conclusion only refers to pre- and perimenopausal patients with (neo)adjuvant tamoxifen pretreatment and with recurrence during or within 12 months after completion of (neo)adjuvant treatment. This population was allocated to research question B2 in dossier assessment A19-06.
ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

3 References

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2. Novartis. Stellungnahme zum IQWiG-Bericht Nr. 752: Ribociclib (Mammakarzinom); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A19-06. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/430/#tab/beschluesse in the document "Zusammenfassende Dokumentation"].

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6. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10.07.2017 [Accessed: 04.01.2019]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

Appendix A – Supplementary results on PFS, time to first chemotherapy, health status and overall survival in the MONALEESA-7 study

A.1 – Results

Table 6: Supplementary results (morbidity, time to event) – RCT, direct comparison: ribociclib + letrozole vs. placebo + letrozole (pre- and perimenopausal women who have received prior endocrine therapy)

Study Outcome category Outcome Time point	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][a]; p-value[b]
MONALEESA-7					
Second data cut-off 30 November 2018					
Morbidity					
PFS[c]	100	17.9 [12.9; 24.2] 66 (66.0)	105	9.2 [5.5; 14.5] 79 (75.2)	0.59 [0.42; 0.83]; 0.002
Time to first subsequent chemotherapy[d]	100	26.0 [22.8; 33.8] 56 (56.0)	105	17.2 [11.3; 25.4] 73 (69.5)	0.67 [0.47; 0.95]; 0.022
Health status (EQ-5D VAS[e])					
Deterioration by ≥ 7 points	100	27.6 [15.0; 33.1] 43 (43.0)	105	33.1 [21.0; NC] 32 (30.5)	1.11 [0.69; 1.77]; 0.652
Deterioration by ≥ 10 points	100	30.4 [15.0; NC] 41 (41.0)	105	33.1 [21.0; NC] 31 (29.5)	1.14 [0.71; 1.83]; 0.584

a: Hazard ratio from Cox regression model stratified by the presence of liver and/or lung metastases (yes vs. no), prior chemotherapy in the advanced setting (yes vs. no) and endocrine combination partner (tamoxifen vs. NSAI).
b: 2-sided log-rank test stratified by the presence of liver and/or lung metastases, prior chemotherapy in the advanced setting and endocrine combination partner (tamoxifen and goserelin vs. NSAI and goserelin).
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: 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.

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; NC: not calculable; NSAI: nonsteroidal aromatase inhibitor; PFS: progression-free survival; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumours; VAS: visual analogue scale; vs.: versus

Table 7: Results (mortality, time to event) – RCT, direct comparison: ribociclib + letrozole vs. placebo + letrozole (total population)

Study **Outcome category**	**Ribociclib + letrozole**		**Placebo + letrozole**		**Ribociclib + letrozole vs. placebo + letrozole**
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-7					
Second data cut-off 30 November 2018					
Mortality					
Overall survival	335	NA 83 (24.8)	337	40.9 [37.8; NC] 109 (32.3)	0.71 [0.54; 0.948]; 0.019

a: Hazard ratio from Cox regression model stratified by the presence of liver and/or lung metastases, prior chemotherapy in the advanced setting and endocrine combination partner (tamoxifen vs. NSAI).
b: 2-sided p-value log-rank test stratified by the presence of liver and/or lung metastases, prior chemotherapy in the advanced setting and endocrine combination partner (tamoxifen vs. NSAI).
CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; NC: not calculable; NSAI: nonsteroidal aromatase inhibitor; RCT: randomized controlled trial; vs.: versus

Table 8: Subgroups (mortality, time to event) – RCT, direct comparison: ribociclib + letrozole vs. placebo + letrozole (total population)

Study Outcome Characteristic Subgroup	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][a]	 p-value[b]
MONALEESA-7						
Second data cut-off 30 November 2018						
Mortality						
Overall survival						
Ethnicity						
Asian	99	NA 16 (16.2)	99	NA [31.6; NC] 37 (37.4)	0.39 [0.22; 0.72]	0.002
Non-Asian	200	NA 57 (28.5)	213	40.9 [37.8; NC] 65 (30.5)	0.91 [0.64; 1.30]	0.609
Total					Interaction:	0.007[c]

a: Hazard ratio from Cox regression model stratified by the presence of liver and/or lung metastases (yes vs. no), prior chemotherapy in the advanced setting (yes vs. no) and endocrine combination partner (tamoxifen vs. NSAI).
b: p-value from 2-sided log-rank test stratified by the presence of liver and/or lung metastases (yes vs. no), prior chemotherapy in the advanced setting (yes vs. no) and endocrine combination partner (tamoxifen vs. NSAI).
c: p-value based on an extension of the Cox regression model by corresponding subgroup variable and the interaction term treatment*subgroup variable.
CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; NC: not calculable; NSAI: nonsteroidal aromatase inhibitor; RCT: randomized controlled trial; vs.: versus

A.2 – Graphic display of the event time analyses presented as supplementary information (Kaplan-Meier curves)

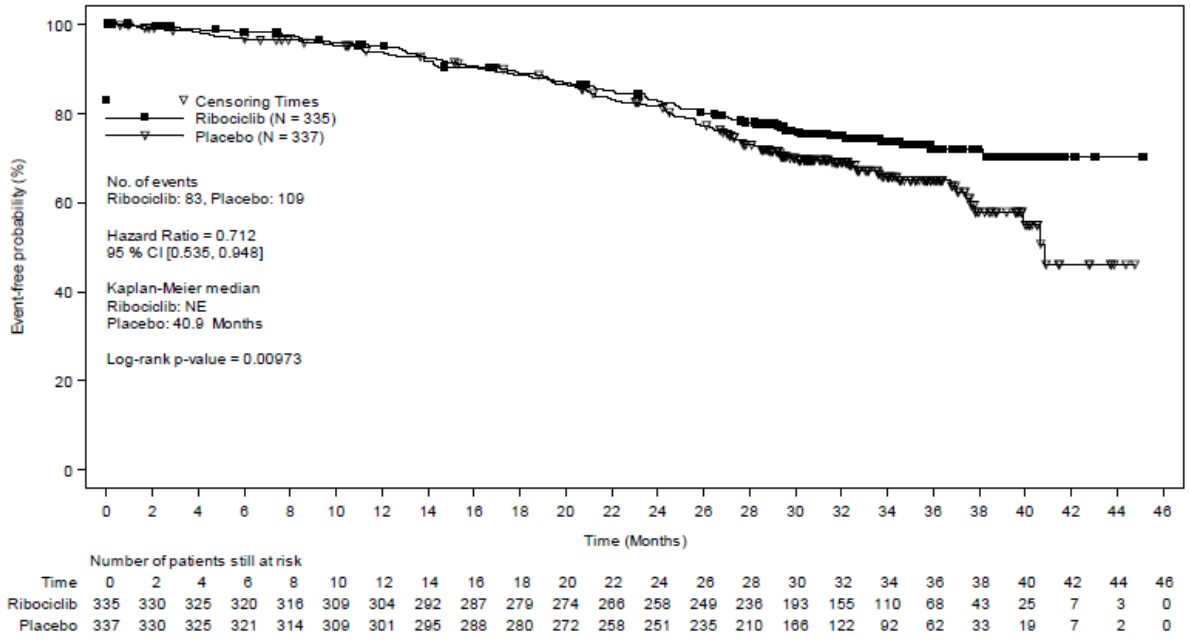


Figure 1: Kaplan-Meier curve on overall survival (total population)

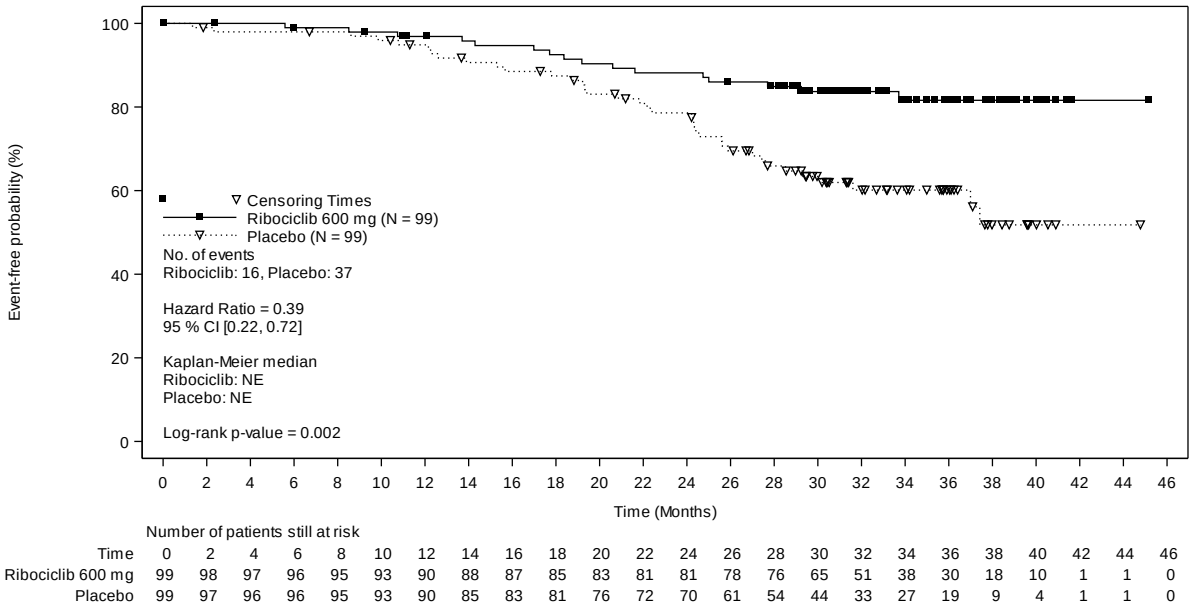
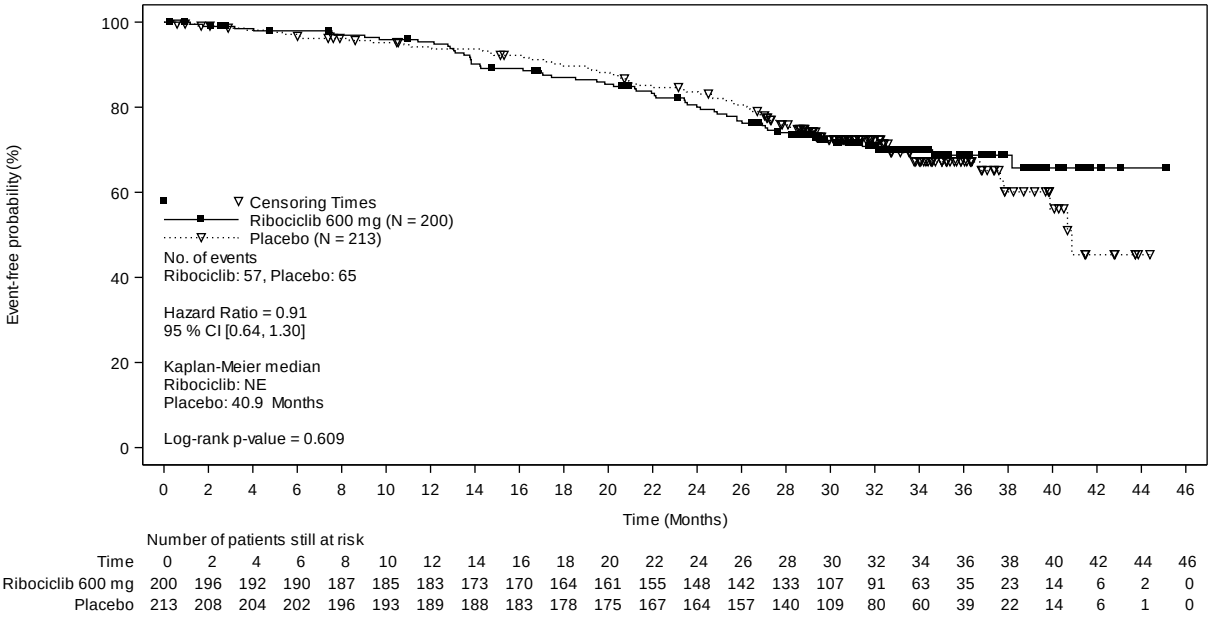


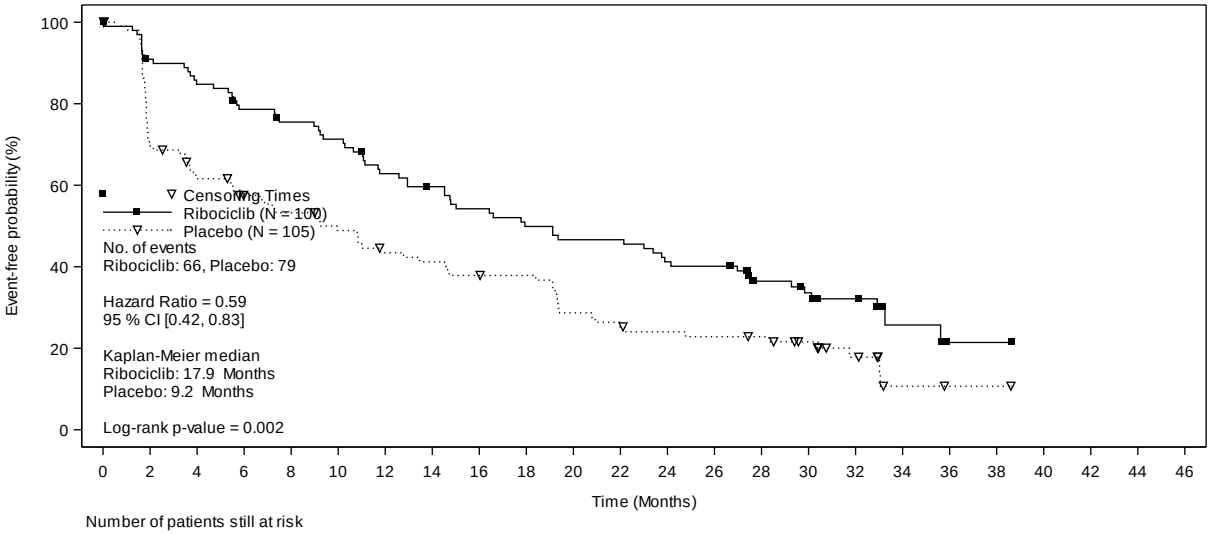
Figure 2: Kaplan-Meier curve on overall survival, subgroup: Asian ethnicity



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
Ribociclib 600 mg	200	196	192	190	187	185	183	173	170	164	161	155	148	142	133	107	91	63	35	23	14	6	2	0
Placebo	213	208	204	202	196	193	189	188	183	178	175	167	164	157	140	109	80	60	39	22	14	6	1	0

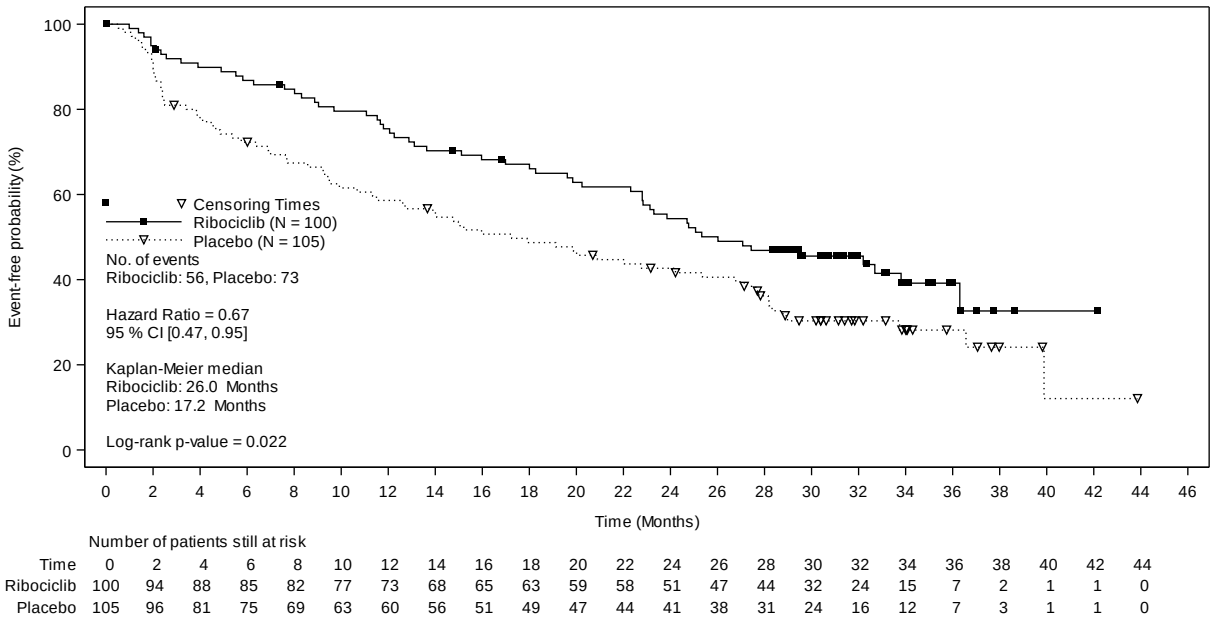
Figure 3: Kaplan-Meier curve on overall survival, subgroup: other ethnicities (non-Asian)



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
Ribociclib	100	89	83	76	72	68	59	55	50	46	43	43	38	37	26	23	16	6	1	1	0
Placebo	105	72	61	54	50	45	39	37	34	33	25	22	20	19	18	14	8	2	1	1	0

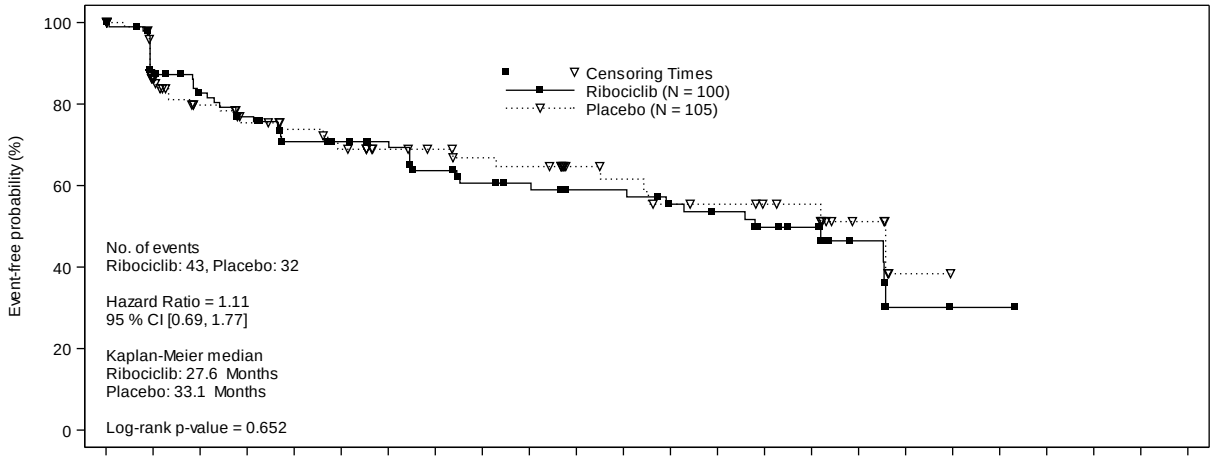
Figure 4: Kaplan-Meier curve on the outcome “PFS” (subpopulation)



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
Ribociclib	100	94	88	85	82	77	73	68	65	63	59	58	51	47	44	32	24	15	7	2	1	1	0
Placebo	105	96	81	75	69	63	60	56	51	49	47	44	41	38	31	24	16	12	7	3	1	1	0

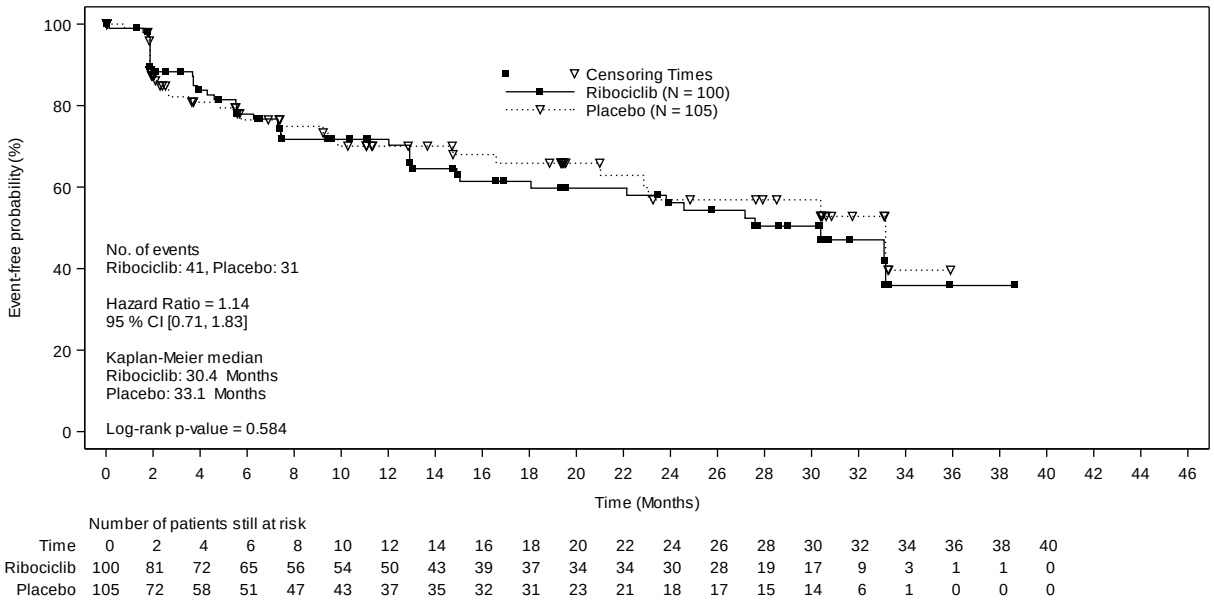
Figure 5: Kaplan-Meier curve on the outcome “time to first subsequent chemotherapy” (subpopulation)



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
Ribociclib	100	80	71	65	56	54	50	43	39	37	34	34	30	28	19	17	9	3	1	1	0
Placebo	105	71	57	50	46	42	36	34	31	30	22	20	17	16	14	13	6	1	0	0	0

Figure 6: Kaplan-Meier curve on the outcome “health status” (EQ-5D VAS – time to deterioration by ≥ 7 points), subpopulation

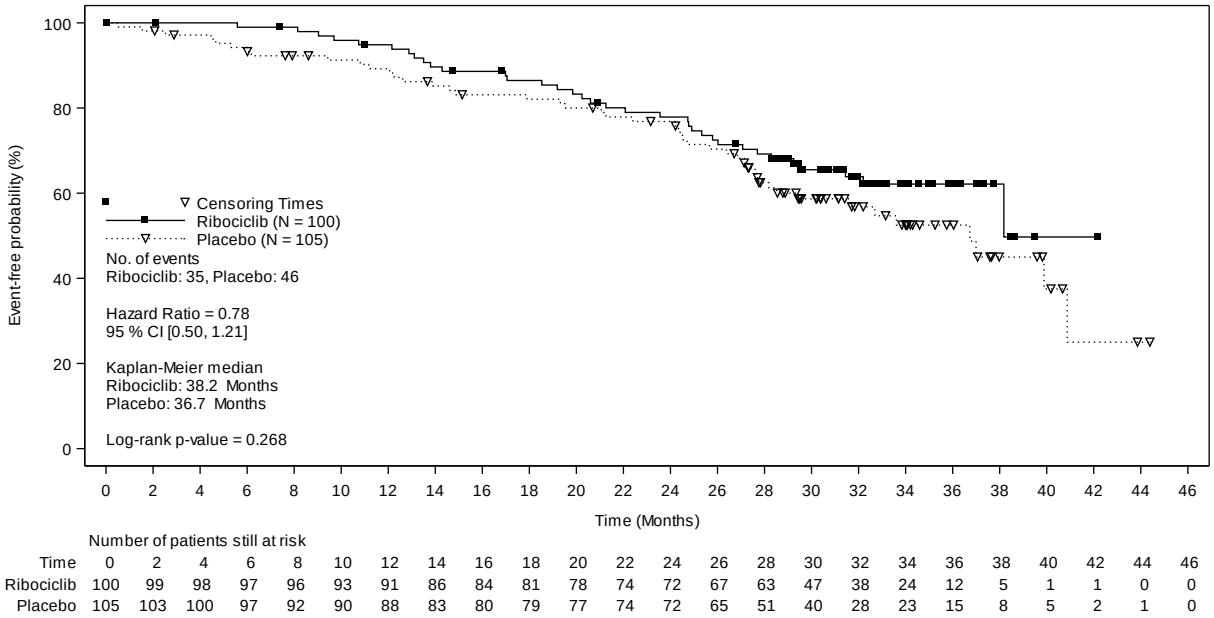


Number of patients still at risk

Time	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40
Ribociclib	100	81	72	65	56	54	50	43	39	37	34	34	30	28	19	17	9	3	1	1	0
Placebo	105	72	58	51	47	43	37	35	32	31	23	21	18	17	15	14	6	1	0	0	0

Figure 7: Kaplan-Meier curve on the outcome “health status” (EQ-5D VAS – time to deterioration by ≥ 10 points), subpopulation

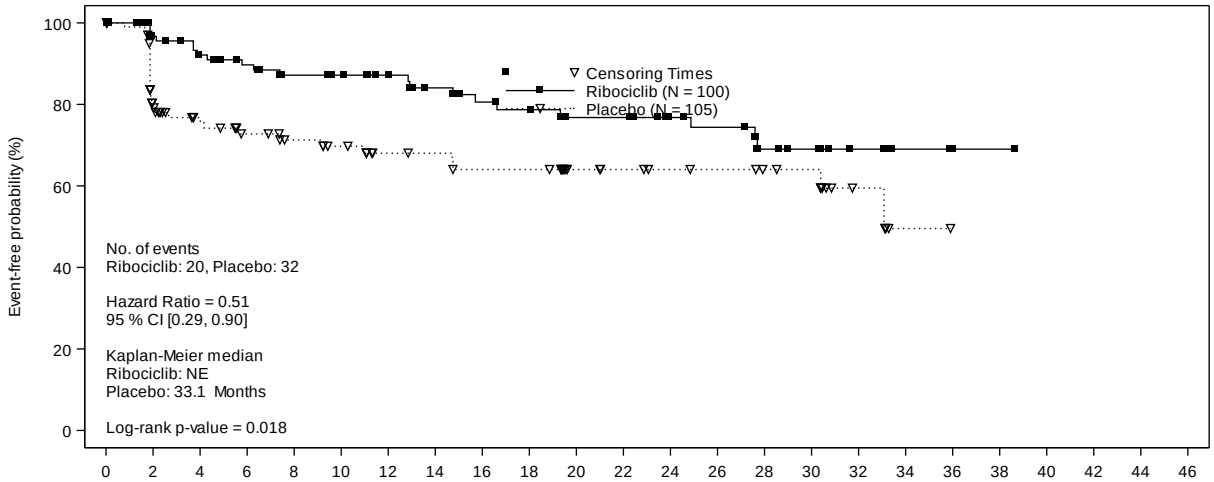
Appendix B – Graphic display of the event time analyses presented in the benefit assessment (Kaplan-Meier curves)



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
Ribociclib	100	99	98	97	96	93	91	86	84	81	78	74	72	67	63	47	38	24	12	5	1	1	0	0
Placebo	105	103	100	97	92	90	88	83	80	79	77	74	72	65	51	40	28	23	15	8	5	2	1	0

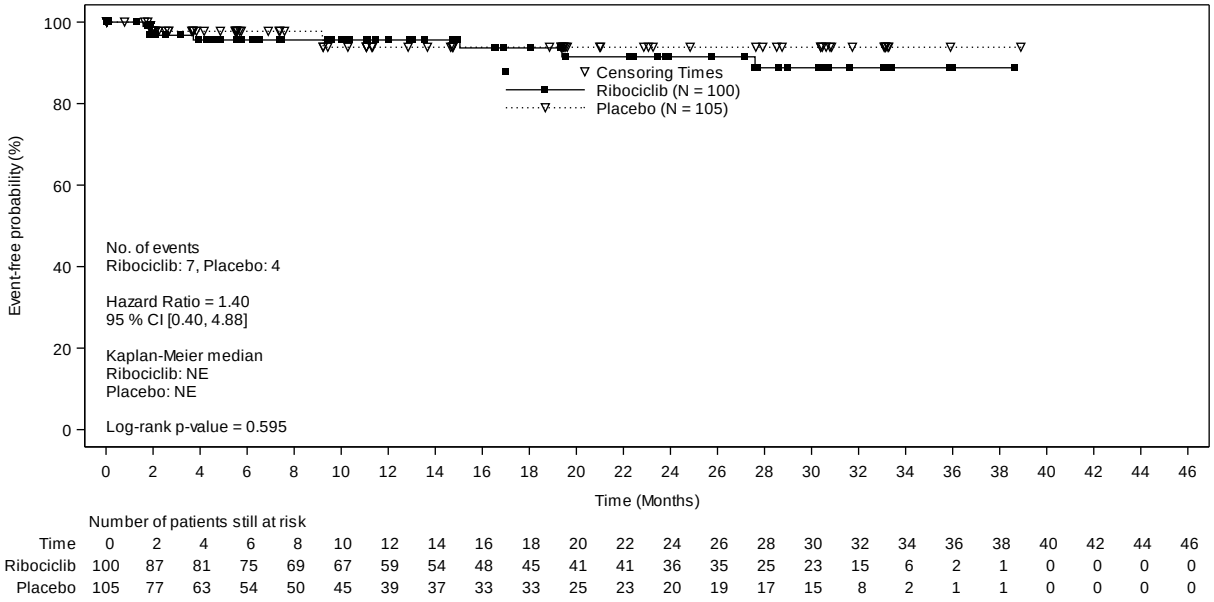
Figure 8: Kaplan-Meier curve on the outcome “overall survival” (subpopulation)



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
Ribociclib	100	86	78	72	65	63	57	51	44	42	38	38	33	31	22	20	13	5	2	1	0
Placebo	105	71	59	51	46	42	35	34	31	31	22	20	18	17	15	14	6	1	0	0	0

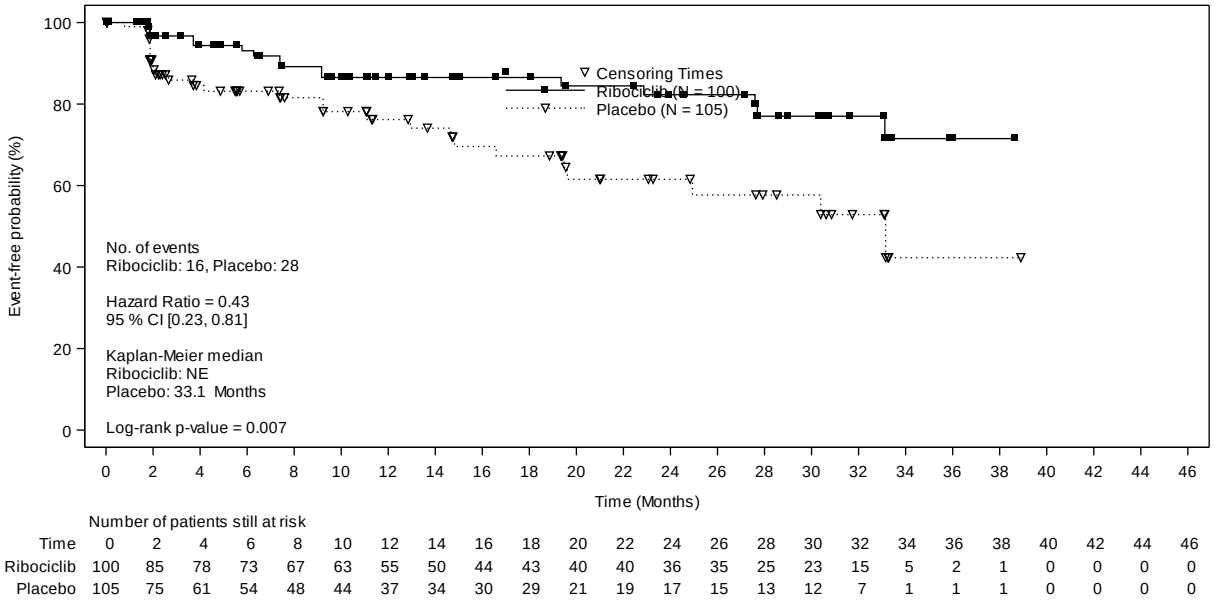
Figure 9: Kaplan-Meier curve on symptoms, outcome “fatigue” (EORTC QLQ-C30, definitive deterioration by ≥ 10 points), subpopulation



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
Ribociclib	100	87	81	75	69	67	59	54	48	45	41	41	36	35	25	23	15	6	2	1	0	0	0	0
Placebo	105	77	63	54	50	45	39	37	33	33	25	23	20	19	17	15	8	2	1	1	0	0	0	0

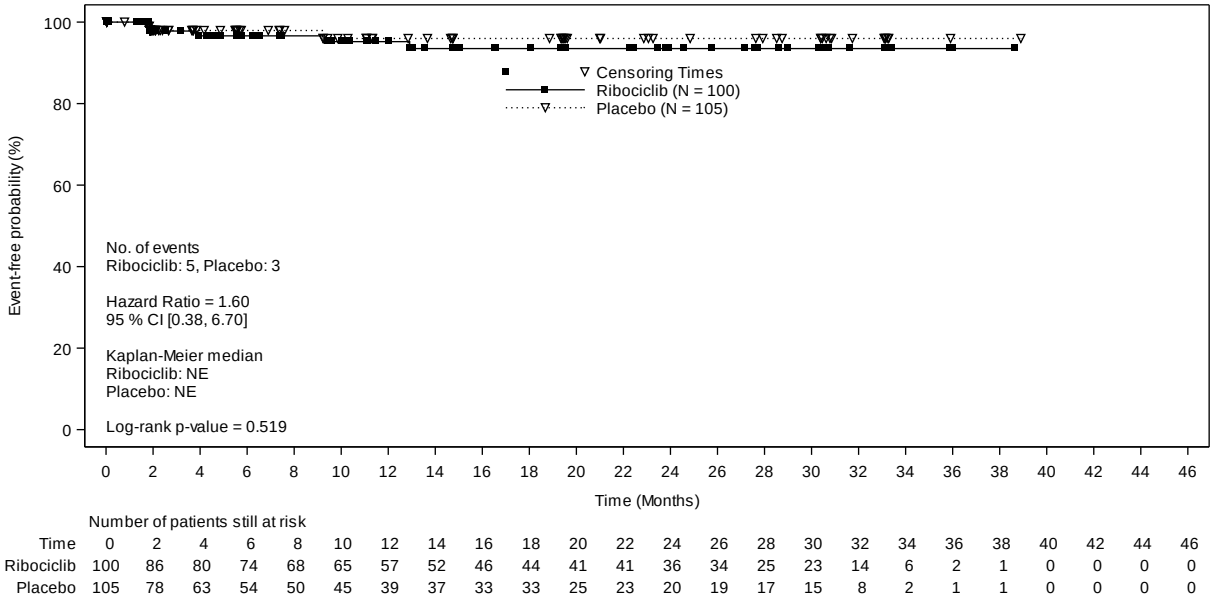
Figure 10: Kaplan-Meier curve on symptoms, outcome “nausea/vomiting” (EORTC QLQ-C30, definitive deterioration by ≥ 10 points), subpopulation



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
Ribociclib	100	85	78	73	67	63	55	50	44	43	40	40	36	35	25	23	15	5	2	1	0	0	0	0
Placebo	105	75	61	54	48	44	37	34	30	29	21	19	17	15	13	12	7	1	1	1	0	0	0	0

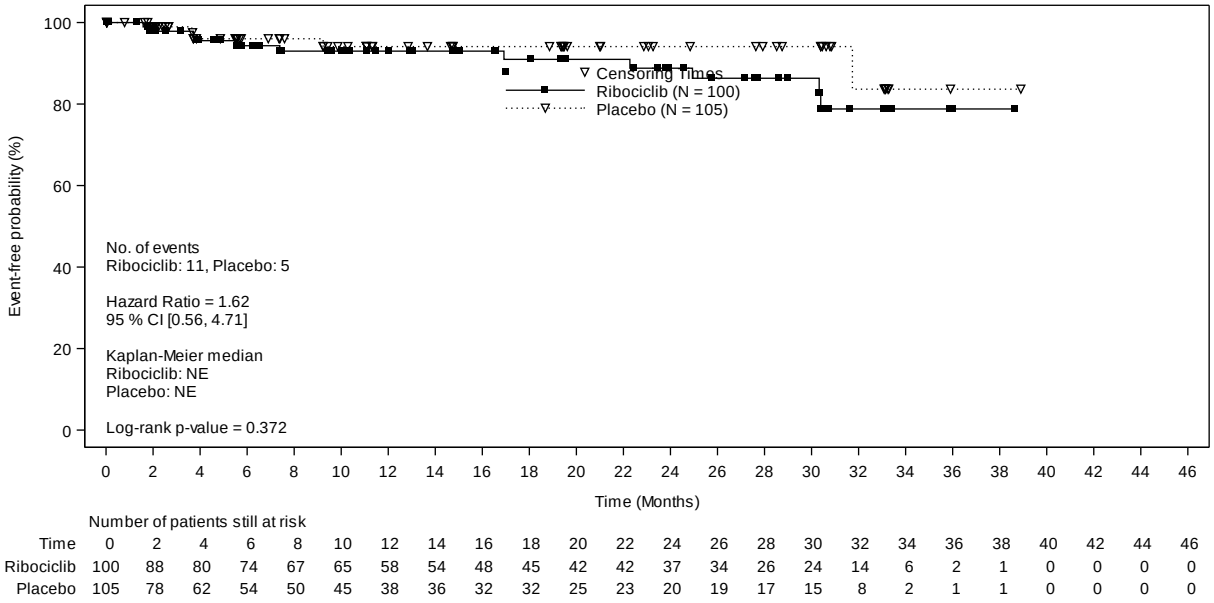
Figure 11: Kaplan-Meier curve on symptoms, outcome “pain” (EORTC QLQ-C30, definitive deterioration by ≥ 10 points), subpopulation



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
Ribociclib	100	86	80	74	68	65	57	52	46	44	41	41	36	34	25	23	14	6	2	1	0	0	0	0
Placebo	105	78	63	54	50	45	39	37	33	33	25	23	20	19	17	15	8	2	1	1	0	0	0	0

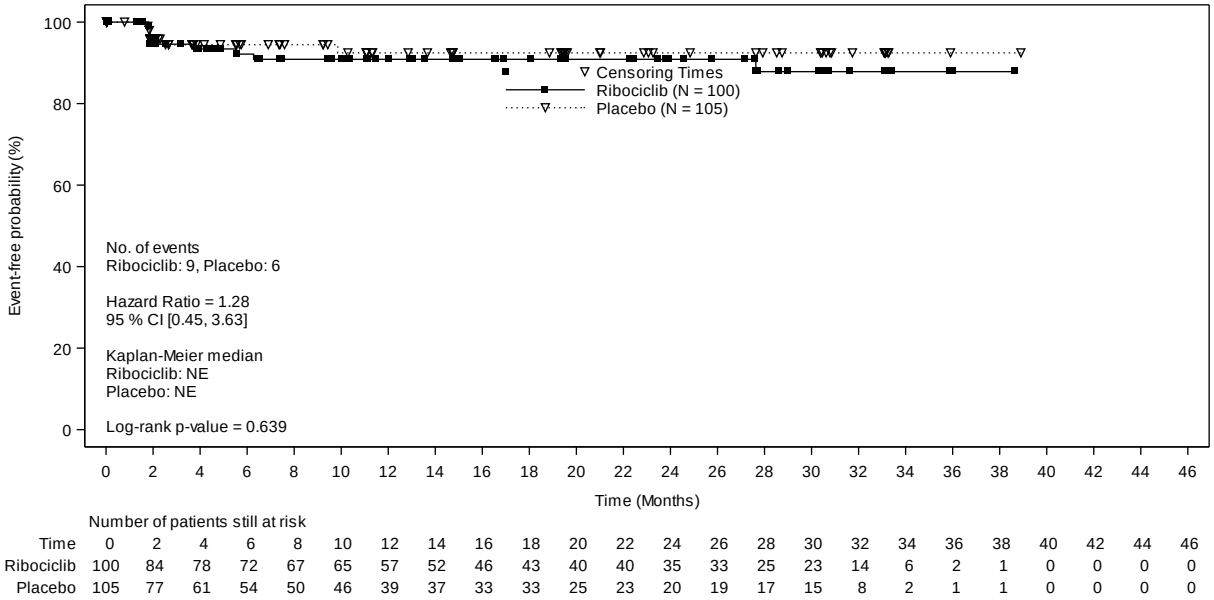
Figure 12: Kaplan-Meier curve on symptoms, outcome “dyspnoea” (EORTC QLQ-C30, definitive deterioration by ≥ 10 points), subpopulation



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
Ribociclib	100	88	80	74	67	65	58	54	48	45	42	42	37	34	26	24	14	6	2	1	0	0	0	0
Placebo	105	78	62	54	50	45	38	36	32	32	25	23	20	19	17	15	8	2	1	1	0	0	0	0

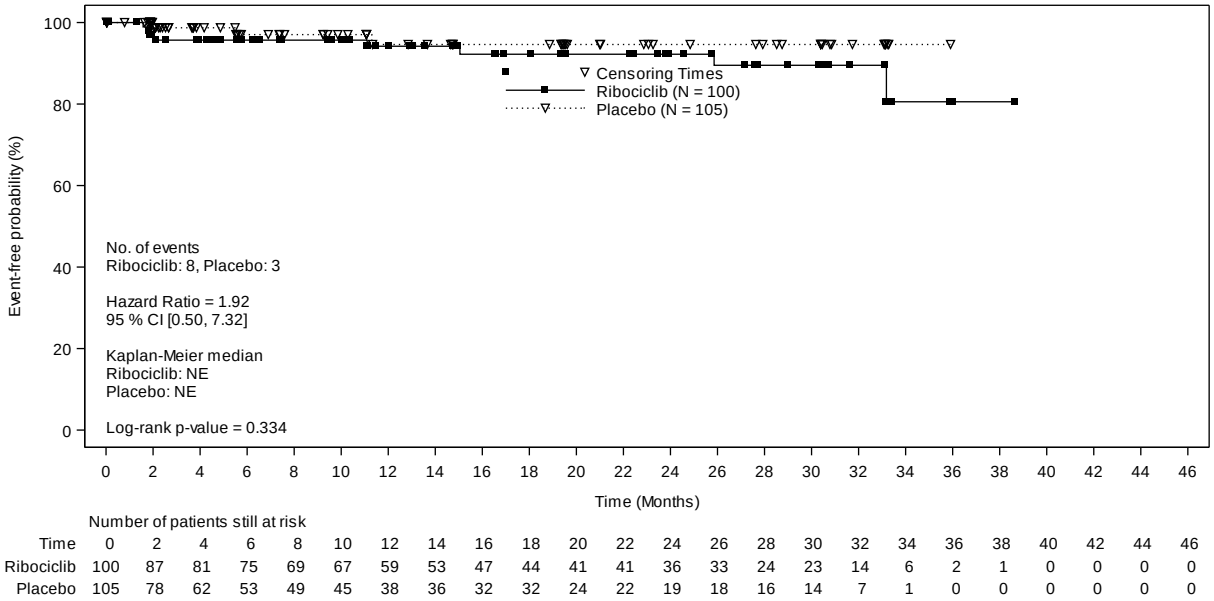
Figure 13: Kaplan-Meier curve on symptoms, outcome “insomnia” (EORTC QLQ-C30, definitive deterioration by ≥ 10 points), subpopulation



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
Ribociclib	100	84	78	72	67	65	57	52	46	43	40	40	35	33	25	23	14	6	2	1	0	0	0	0
Placebo	105	77	61	54	50	46	39	37	33	33	25	23	20	19	17	15	8	2	1	1	0	0	0	0

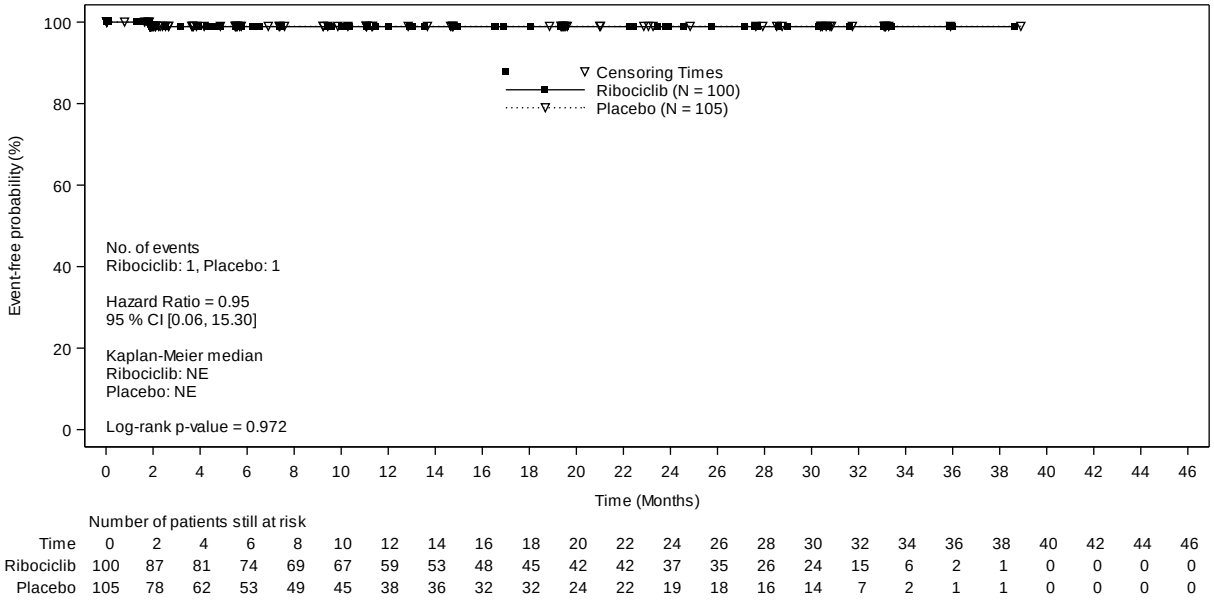
Figure 14: Kaplan-Meier curve on symptoms, outcome “appetite loss” (EORTC QLQ-C30, definitive deterioration by ≥ 10 points), subpopulation



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
Ribociclib	100	87	81	75	69	67	59	53	47	44	41	41	36	33	24	23	14	6	2	1	0	0	0	0
Placebo	105	78	62	53	49	45	38	36	32	32	24	22	19	18	16	14	7	1	0	0	0	0	0	0

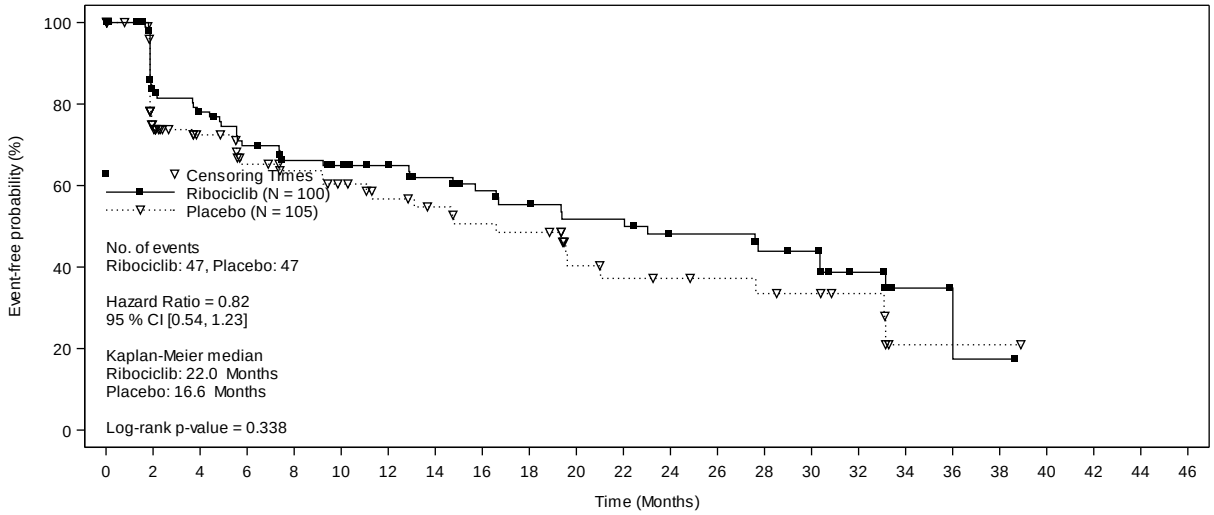
Figure 15: Kaplan-Meier curve on symptoms, outcome “constipation” (EORTC QLQ-C30, definitive deterioration by ≥ 10 points), subpopulation



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
Ribociclib	100	87	81	74	69	67	59	53	48	45	42	42	37	35	26	24	15	6	2	1	0	0	0	0
Placebo	105	78	62	53	49	45	38	36	32	32	24	22	19	18	16	14	7	2	1	1	0	0	0	0

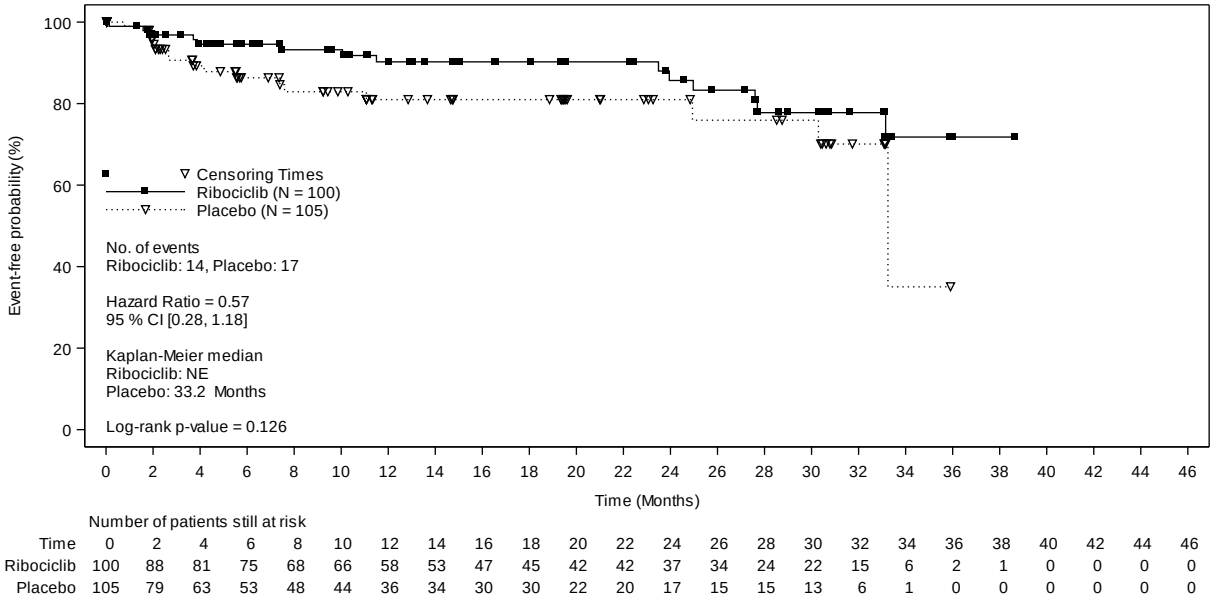
Figure 16: Kaplan-Meier curve on symptoms, outcome “diarrhoea” (EORTC QLQ-C30, definitive deterioration by ≥ 10 points), subpopulation



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
Ribociclib	100	75	67	59	53	50	45	40	35	32	29	29	25	25	19	18	11	5	2	1	0
Placebo	105	66	53	43	39	35	30	27	24	23	14	12	11	10	9	8	6	1	1	1	0

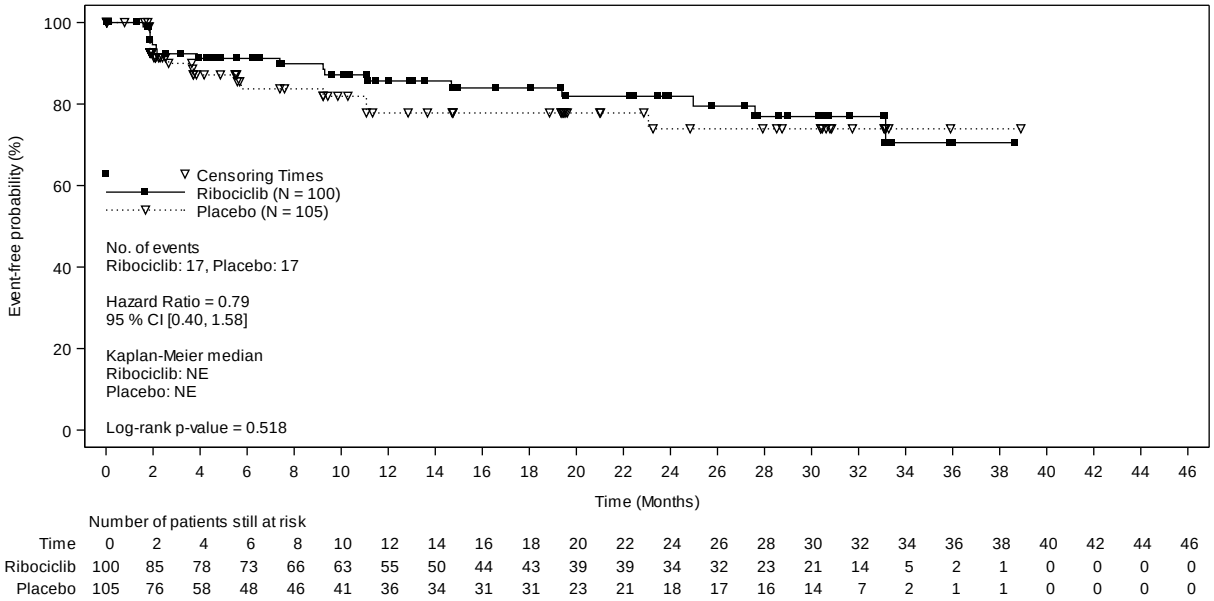
Figure 17: Kaplan-Meier curve on symptoms, outcome “side effects of systemic treatment” (EORTC QLQ-BR23, definitive deterioration by ≥ 10 points), subpopulation



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
Ribociclib	100	88	81	75	68	66	58	53	47	45	42	42	37	34	24	22	15	6	2	1	0	0	0	0
Placebo	105	79	63	53	48	44	36	34	30	30	22	20	17	15	15	13	6	1	0	0	0	0	0	0

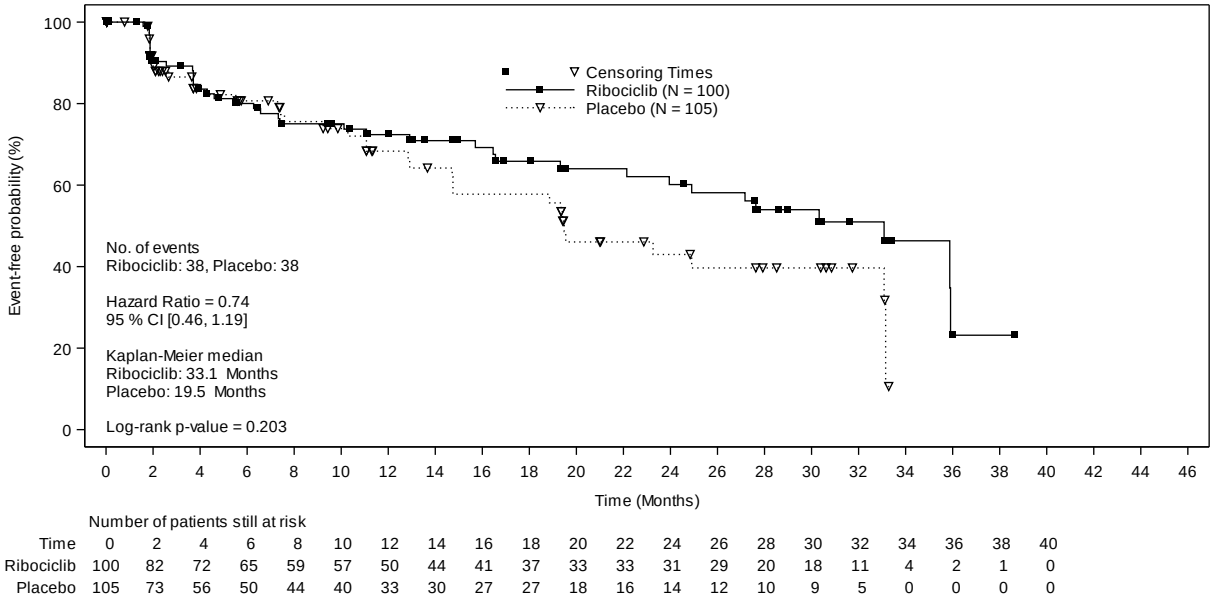
Figure 18: Kaplan-Meier curve on symptoms, outcome “symptoms in chest region” (EORTC QLQ-BR23, definitive deterioration by ≥ 10 points), subpopulation



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
Ribociclib	100	85	78	73	66	63	55	50	44	43	39	39	34	32	23	21	14	5	2	1	0	0	0	0
Placebo	105	76	58	48	46	41	36	34	31	31	23	21	18	17	16	14	7	2	1	1	0	0	0	0

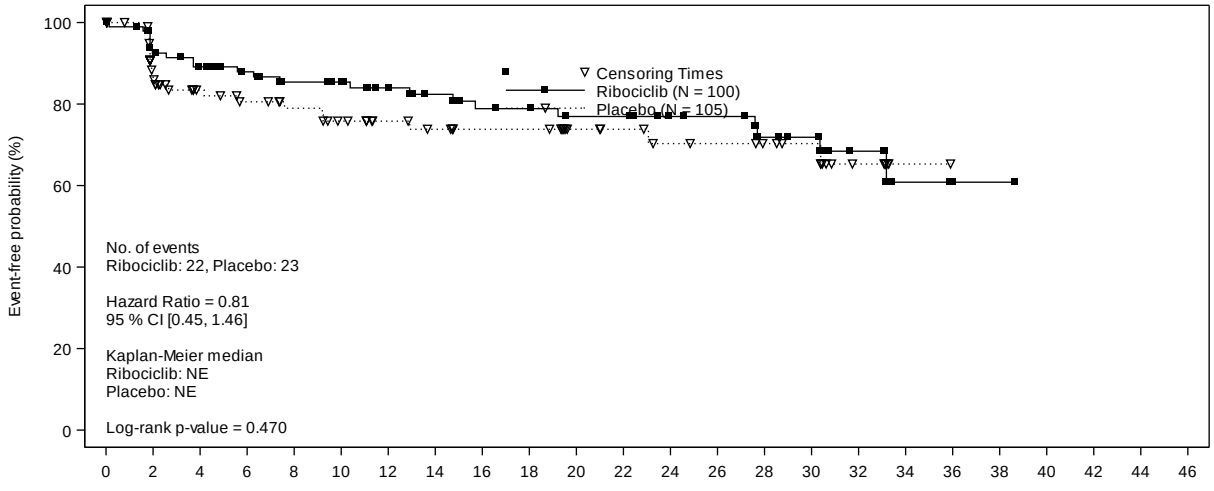
Figure 19: Kaplan-Meier curve on symptoms, outcome “symptoms in arm region” (EORTC QLQ-BR23, definitive deterioration by ≥ 10 points), subpopulation



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
Ribociclib	100	82	72	65	59	57	50	44	41	37	33	33	31	29	20	18	11	4	2	1	0
Placebo	105	73	56	50	44	40	33	30	27	27	18	16	14	12	10	9	5	0	0	0	0

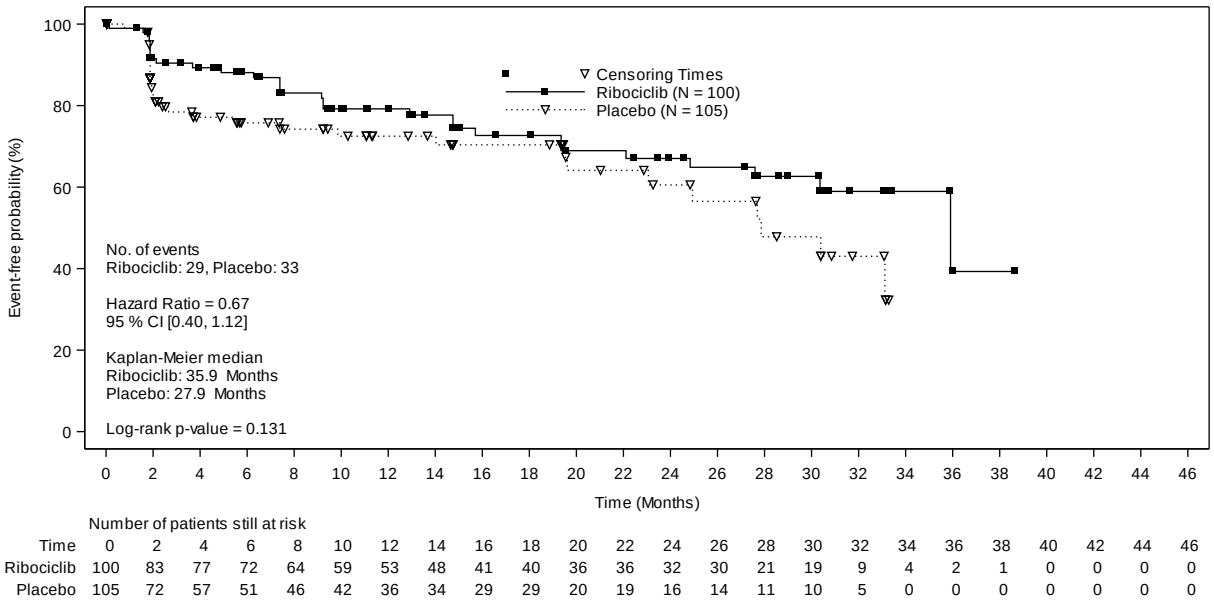
Figure 20: Kaplan-Meier curve on health-related quality of life, outcome "health status" (EORTC QLQ-C30, definitive deterioration by ≥ 10 points), subpopulation



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
Ribociclib	100	84	77	71	64	62	54	49	43	42	39	39	35	34	24	22	13	5	2	1	0	0	0	0
Placebo	105	73	59	54	50	45	39	36	32	32	24	22	19	18	16	14	7	1	0	0	0	0	0	0

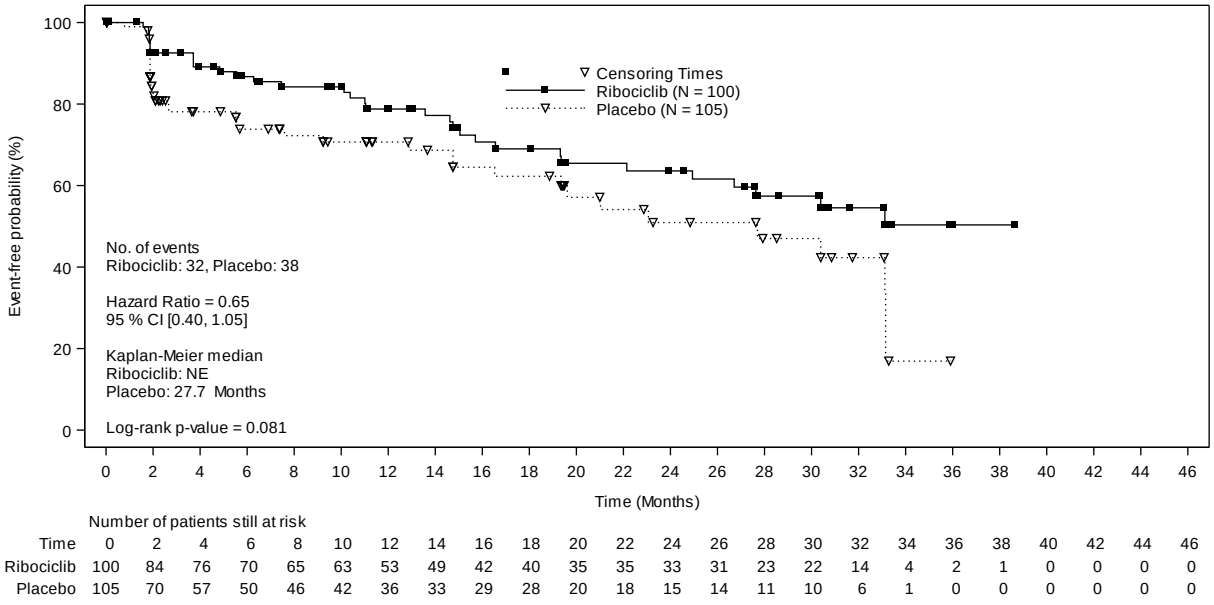
Figure 21: Kaplan-Meier curve on health-related quality of life, outcome "physical functioning" (EORTC QLQ-C30, definitive deterioration by ≥ 10 points), subpopulation



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
Ribociclib	100	83	77	72	64	59	53	48	41	40	36	36	32	30	21	19	9	4	2	1	0	0	0	0
Placebo	105	72	57	51	46	42	36	34	29	29	20	19	16	14	11	10	5	0	0	0	0	0	0	0

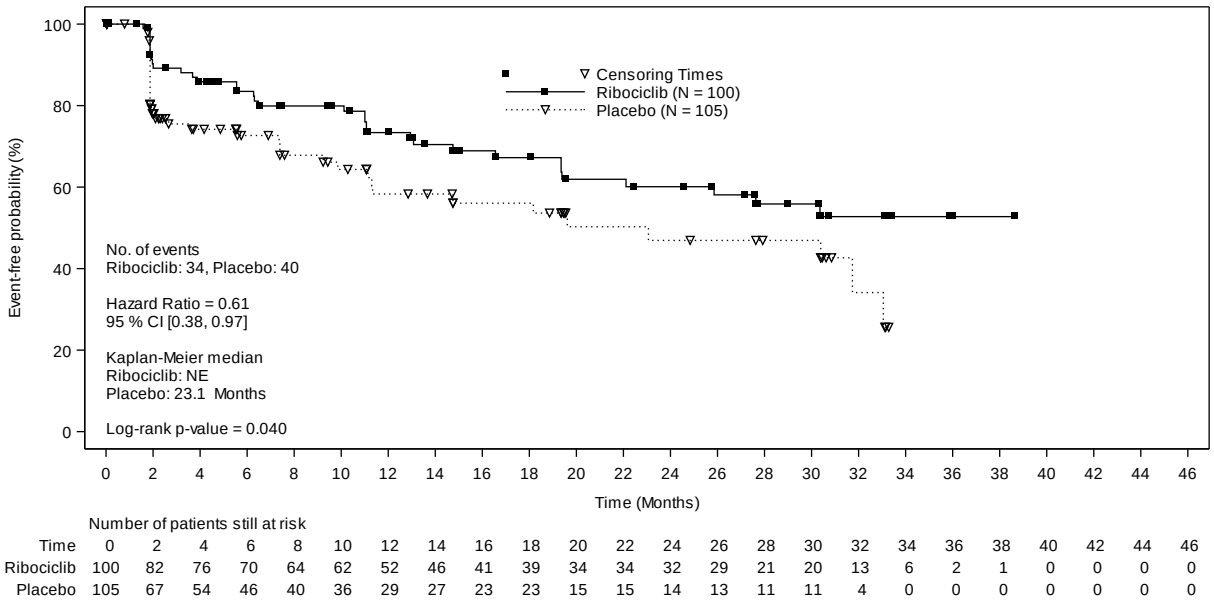
Figure 22: Kaplan-Meier curve on health-related quality of life, outcome “role functioning” (EORTC QLQ-C30, definitive deterioration by ≥ 10 points), subpopulation



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
Ribociclib	100	84	76	70	65	63	53	49	42	40	35	35	33	31	23	22	14	4	2	1	0	0	0	0
Placebo	105	70	57	50	46	42	36	33	29	28	20	18	15	14	11	10	6	1	0	0	0	0	0	0

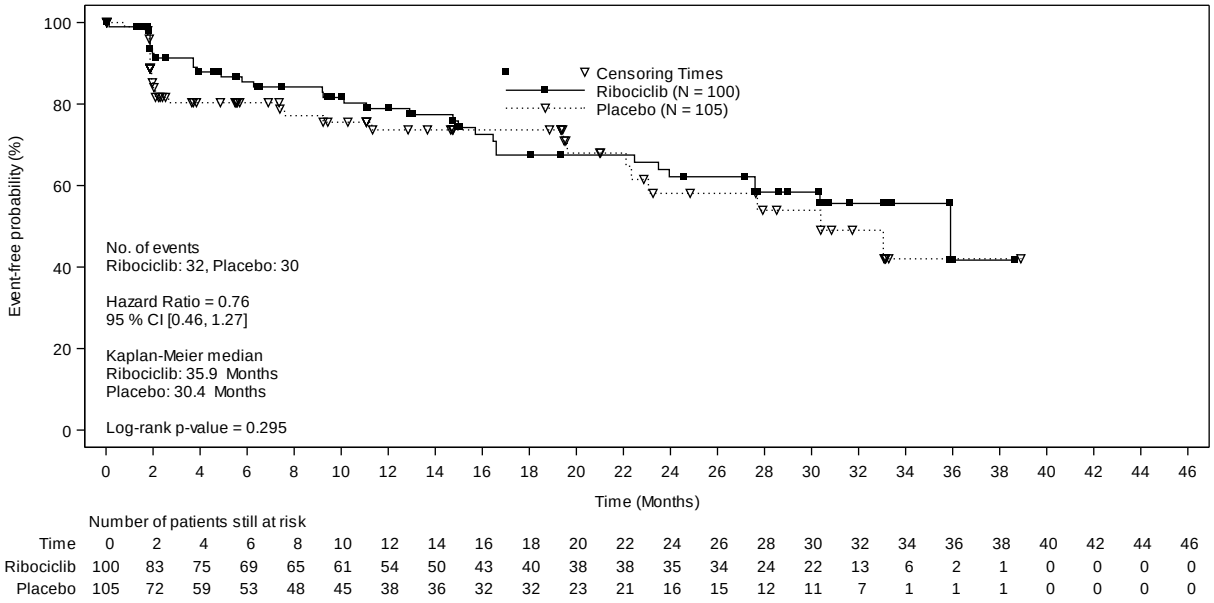
Figure 23: Kaplan-Meier curve on health-related quality of life, outcome “emotional functioning” (EORTC QLQ-C30, definitive deterioration by ≥ 10 points), subpopulation



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
Ribociclib	100	82	76	70	64	62	52	46	41	39	34	34	32	29	21	20	13	6	2	1	0	0	0	0
Placebo	105	67	54	46	40	36	29	27	23	23	15	15	14	13	11	11	4	0	0	0	0	0	0	0

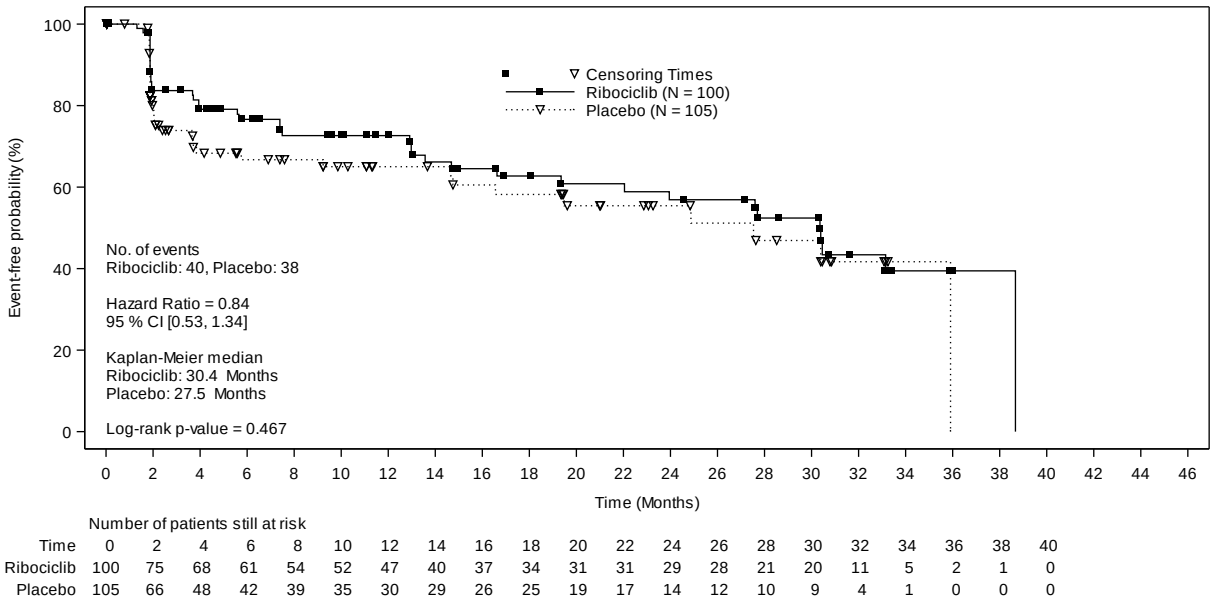
Figure 24: Kaplan-Meier curve on health-related quality of life, outcome "cognitive functioning" (EORTC QLQ-C30, definitive deterioration by ≥ 10 points), subpopulation



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
Ribociclib	100	83	75	69	65	61	54	50	43	40	38	38	35	34	24	22	13	6	2	1	0	0	0	0
Placebo	105	72	59	53	48	45	38	36	32	32	23	21	16	15	12	11	7	1	1	1	0	0	0	0

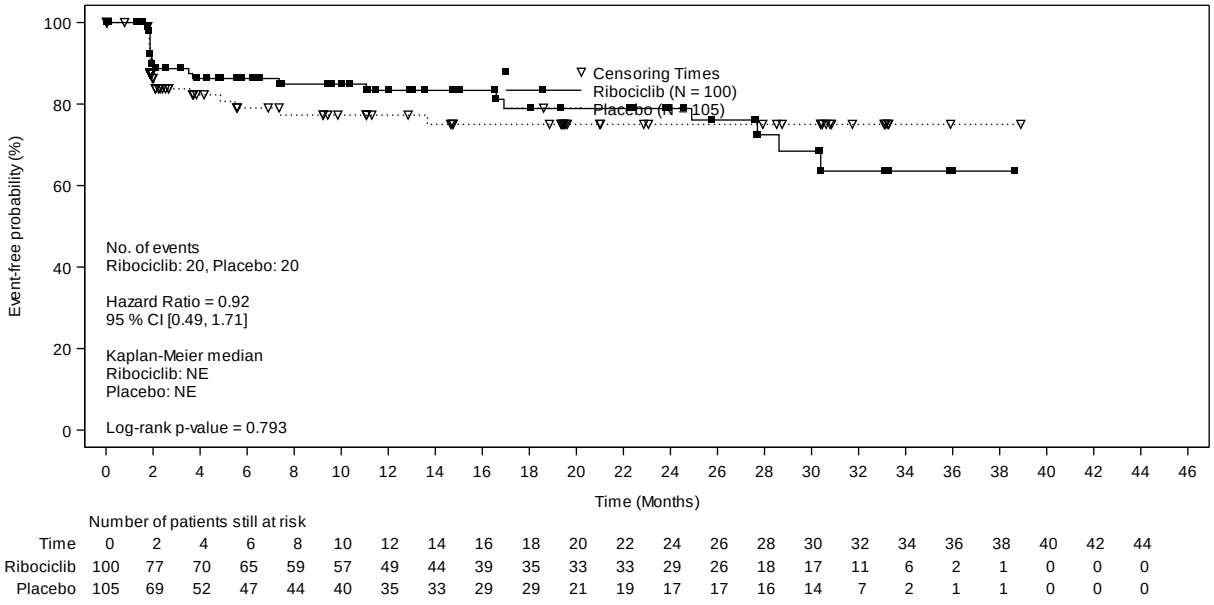
Figure 25: Kaplan-Meier curve on health-related quality of life, outcome "social functioning" (EORTC QLQ-C30, definitive deterioration by ≥ 10 points), subpopulation



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
Ribociclib	100	75	68	61	54	52	47	40	37	34	31	31	29	28	21	20	11	5	2	1	0
Placebo	105	66	48	42	39	35	30	29	26	25	19	17	14	12	10	9	4	1	0	0	0

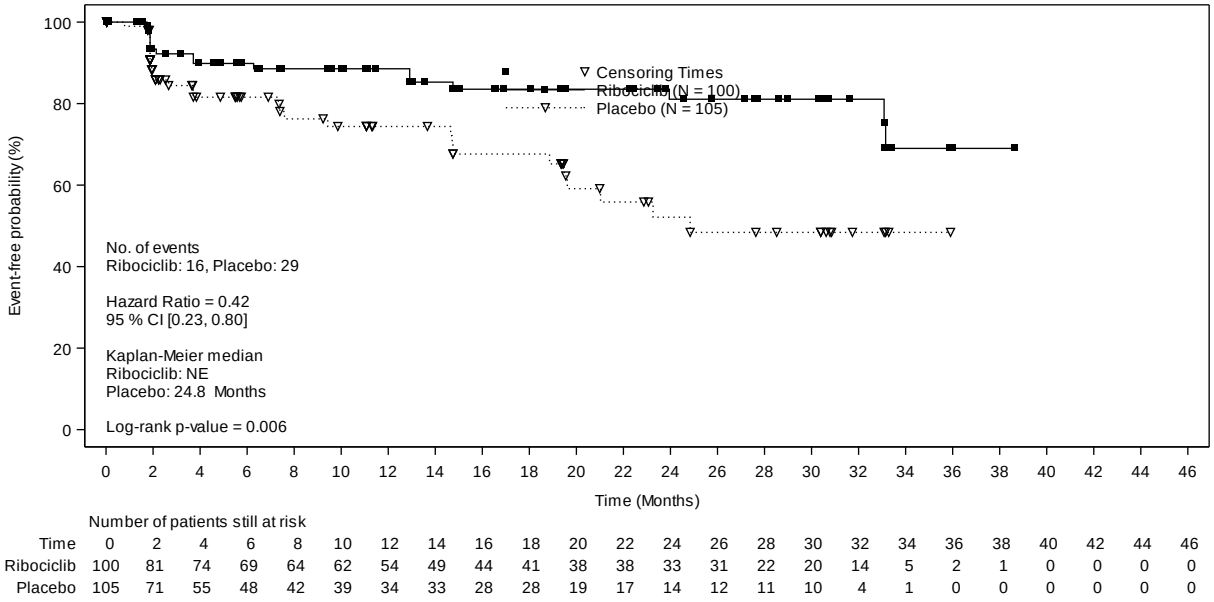
Figure 26: Kaplan-Meier curve on health-related quality of life, outcome “body image” (EORTC QLQ-BR23, definitive deterioration by ≥ 10 points), subpopulation



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
Ribociclib	100	77	70	65	59	57	49	44	39	35	33	33	29	26	18	17	11	6	2	1	0	0	0
Placebo	105	69	52	47	44	40	35	33	29	29	21	19	17	17	16	14	7	2	1	1	0	0	0

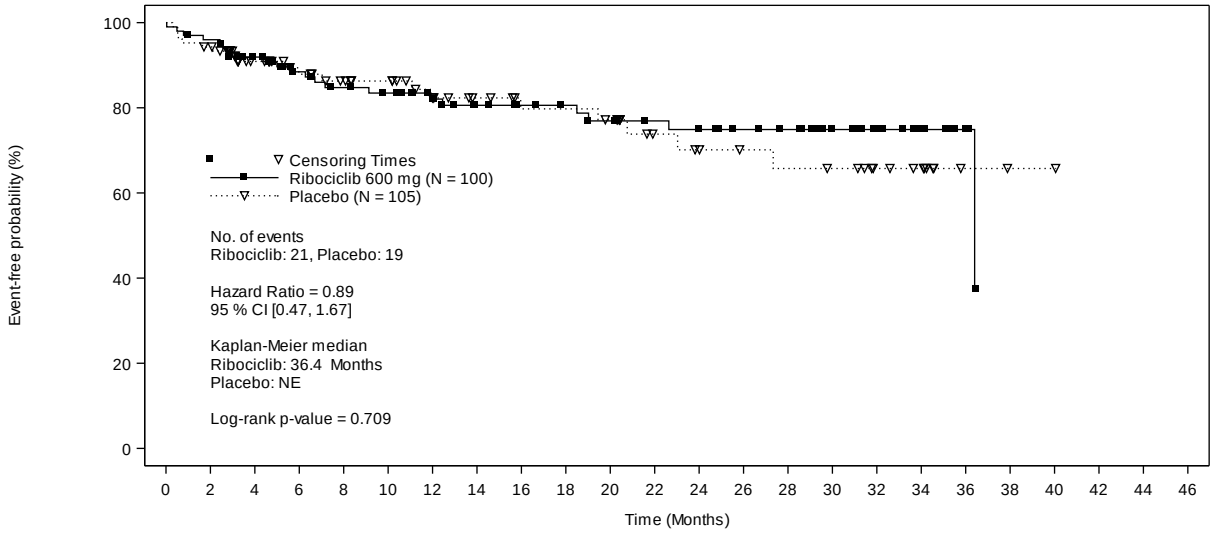
Figure 27: Kaplan-Meier curve on health-related quality of life, outcome “sexual activity” (EORTC QLQ-BR23, definitive deterioration by ≥ 10 points), subpopulation



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
Ribociclib	100	81	74	69	64	62	54	49	44	41	38	38	33	31	22	20	14	5	2	1	0	0	0	0
Placebo	105	71	55	48	42	39	34	33	28	28	19	17	14	12	11	10	4	1	0	0	0	0	0	0

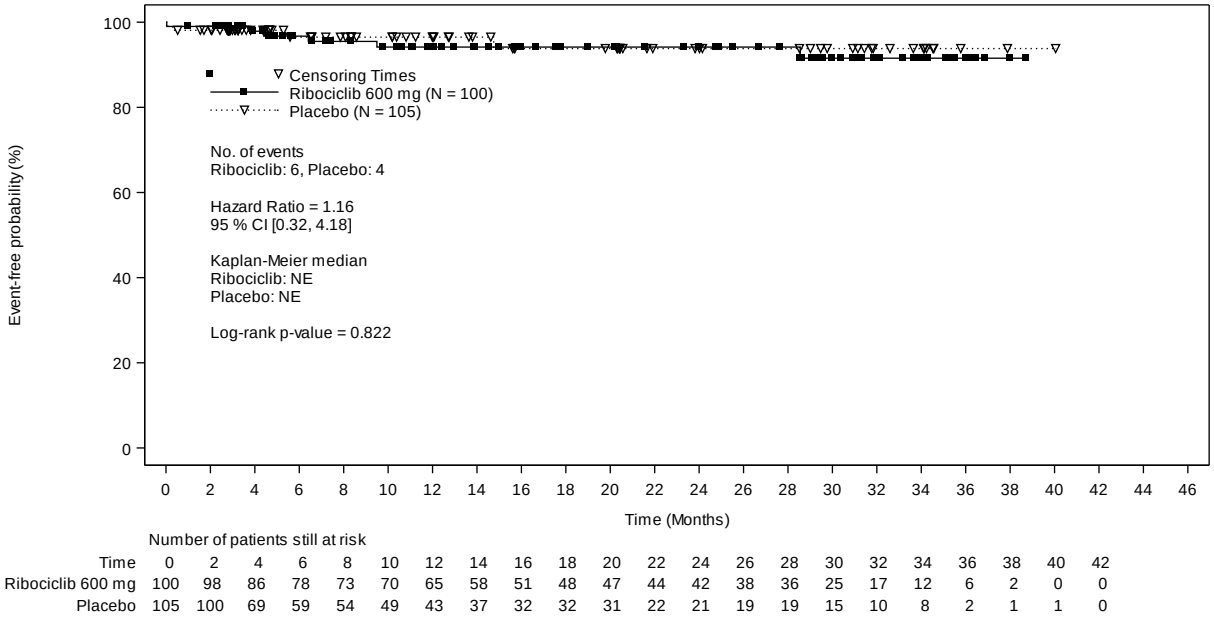
Figure 28: Kaplan-Meier curve on health-related quality of life, outcome “future perspective” (EORTC QLQ-BR23, definitive deterioration by ≥ 10 points), subpopulation



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
Ribociclib 600 mg	100	95	83	73	67	64	58	50	46	44	41	38	36	32	30	22	15	9	4	0	0	0
Placebo	105	98	68	58	52	48	40	35	31	31	29	20	18	16	15	14	10	8	2	1	1	0

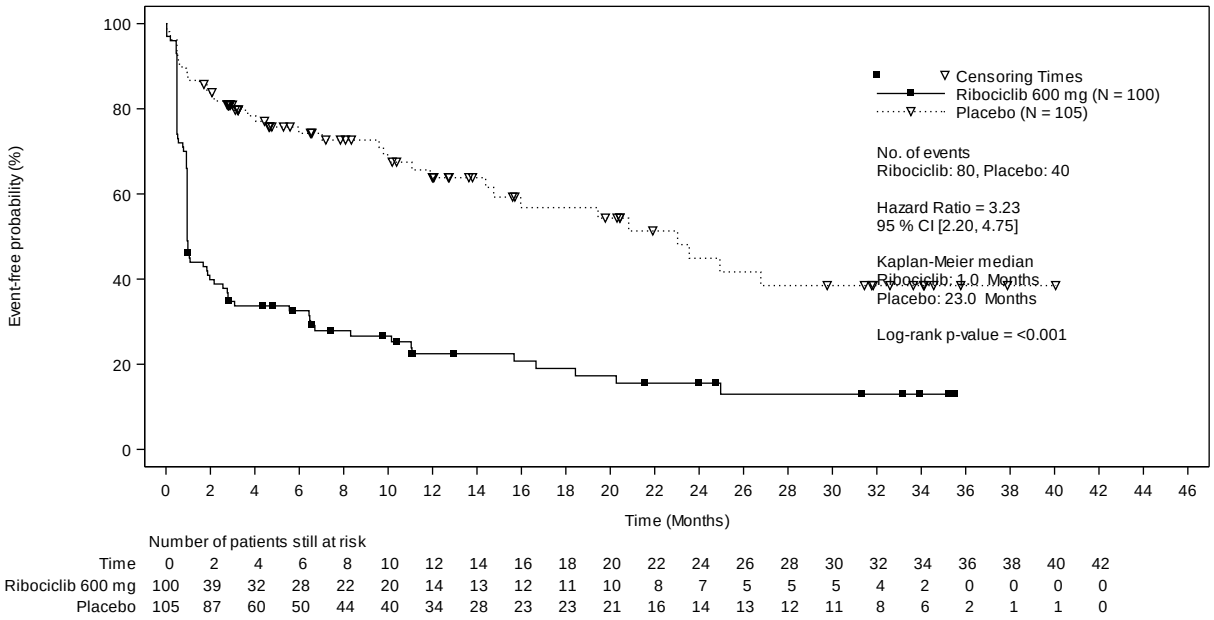
Figure 29: Kaplan-Meier curve on side effects, outcome “SAEs” (subpopulation)



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
Ribociclib 600 mg	100	98	86	78	73	70	65	58	51	48	47	44	42	38	36	25	17	12	6	2	0	0
Placebo	105	100	69	59	54	49	43	37	32	32	31	22	21	19	19	15	10	8	2	1	1	0

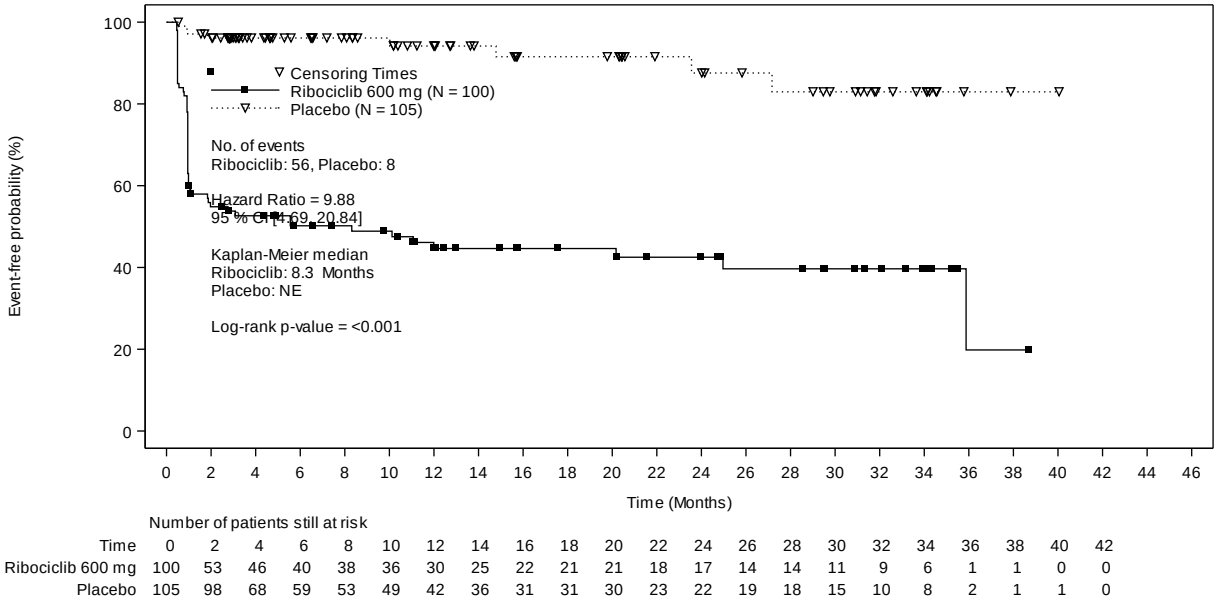
Figure 30: Kaplan-Meier curve on side effects, outcome “discontinuation due to AEs” (subpopulation)



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
Ribociclib 600 mg	100	39	32	28	22	20	14	13	12	11	10	8	7	5	5	5	4	2	0	0	0	0
Placebo	105	87	60	50	44	40	34	28	23	23	21	16	14	13	12	11	8	6	2	1	1	0

Figure 31: Kaplan-Meier curve on side effects, outcome “severe AEs” (CTCAE grade 3–4, subpopulation)



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
Ribociclib 600 mg	100	53	46	40	38	36	30	25	22	21	21	18	17	14	14	11	9	6	1	1	0	0
Placebo	105	98	68	59	53	49	42	36	31	31	30	23	22	19	18	15	10	8	2	1	1	0

Figure 32: Kaplan-Meier curve on side effects, outcome “blood and lymphatic system disorders (SOC, CTCAE grade 3–4, subpopulation)