Clinical Study Report

Study title	A randomized, open-label, multicenter, two-arm, phase III study to evaluate efficacy and quality of life in patients with metastatic hormone receptor-positive HER2-negative breast cancer receiving ribociclib in combination with endocrine therapy or chemotherapy with or without bevacizumab in first line
Document status	Final
Version number	Version 1.0
Date of final version of the study report	22-Aug-2022
Protocol number	IOM-050371
EudraCT number	2017-002930-22
Sponsor	iOMEDICO AG Ellen-Gottlieb-Straße 19 D-79106 Freiburg im Breisgau
Authors of report	[redacted]

This study was performed in compliance with the ICH (International Conference of Harmonization) GCP (Good Clinical Practices) guidelines. Essential documents will be retained in accordance with the ICH-GCP guidelines.

IMPROVE ONCOLOGY

1. Title Page

Study title	A randomized, open-label, multicenter, two-arm, phase III study to evaluate efficacy and quality of life in patients with metastatic hormone receptor-positive HER2-negative breast cancer receiving ribociclib in combination with endocrine therapy or chemotherapy with or without bevacizumab in first line
Short title	RIBBIT
Protocol number	IOM-050371
EudraCT No.	2017-002930-22
Investigational product	Ribociclib (LEE011, Kisqali®) in combination with an aromatase inhibitor or fulvestrant
Comparator	Capecitabine with bevacizumab OR paclitaxel with or without bevacizumab
Indication	Hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, advanced breast cancer (ABC) with visceral metastases
Design	Prospective, randomized, open-label, two-arm, multicenter interventional study
Development phase	Phase III
Sponsor	iOMEDICO AG Ellen-Gottlieb-Straße 19 D-79106 Freiburg im Breisgau
Coordinating investigator	Prof. Dr. Thomas Decker Onkologie Hämatologie Ravensburg Ravensburg, Germany
Study initiation date	24-May-2018
Study termination date	30-Nov-2021

During the study the recruitment rate was persistently and considerably lower than originally expected. In addition, the experimental treatment used in the RIBBIT study evolved to be frequently used in routine clinical practice, thus, the primary scientific question of the study was no longer valid (i.e., whether to choose ribociclib plus endocrine therapy or a chemotherapy-based treatment strategy in the first-line setting for patients with HR-positive, HER2-negative ABC). Therefore, the sponsor decided to end the recruitment prematurely. The study was initially designed to enroll and randomize 158 patients. Recruitment was ended on 28-Dec-2020 following enrollment of 41 patients (38 randomized patients). Last-patient-last-visit took place on 30-Nov-2021, denoting the end of the RIBBIT study.

Authors of report	[redacted]
Version and date of report	Final v1.0, 22-Aug-2022

This study was performed in compliance with the ICH (International Conference of Harmonization) GCP (Good Clinical Practices) guidelines. Essential documents will be retained in accordance with the ICH-GCP guidelines.

2. Synopsis

<table>
<tr><td colspan="2">Name of Sponsor/Company:
iOMEDICO AG</td><td>Volume:
Page:</td><td>(For National Authority Use Only)</td></tr>
<tr><td colspan="2">Name of Finished Product:
Kisqali®</td><td rowspan="2"></td><td rowspan="2"></td></tr>
<tr><td colspan="2">Name of Active Ingredients:
Ribociclib</td></tr>
<tr><td colspan="4">Title of study:
A randomized, open-label, multicenter, two-arm, phase III study to evaluate efficacy and quality of life in patients with metastatic hormone receptor-positive, HER2-negative breast cancer receiving ribociclib in combination with endocrine therapy or chemotherapy with or without bevacizumab in first-line

Short title: RIBBIT</td></tr>
<tr><td colspan="4">Coordinating investigator:
Prof. Dr. med. Thomas Decker, Onkologie Hämatologie Ravensburg, Ravensburg, Germany.</td></tr>
<tr><td colspan="4">Study centers:
In total, 33 study centers in Germany were initiated, of these, 12 centers enrolled patients (refer to section 2.2).</td></tr>
<tr><td colspan="4">Publication (reference):
None.</td></tr>
<tr><td colspan="3">Study period: 24-May-2018 – 30-Nov-2021
First-patient-in (date of first enrollment): 24-May-2018
Last-patient-in (date of last enrollment): 28-Dec-2020
Last-patient-out (end of treatment): 31-Oct-2021
Last-patient-last-visit (end of safety follow-up): 30-Nov-2021</td><td>Phase of development:
Phase III</td></tr>
<tr><td colspan="4">Objectives:
Primary objective
To compare the efficacy in terms of progression-free survival (PFS) of patients receiving ribociclib plus endocrine therapy (ET; arm A) OR chemotherapy (capecitabine plus bevacizumab OR paclitaxel with or without bevacizumab; arm B) as first-line treatment of adult women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer (BC) presenting with visceral metastasis.
Secondary objectives
To assess and compare the two treatment arms with respect to the following efficacy outcomes:
response rates
clinical benefit rate (CBR)
time to response (TTR)
overall survival (OS)
To determine safety and tolerability in the two treatment arms in terms of (serious) adverse events ((S)AEs), Eastern Cooperative Oncology Group (ECOG) performance status, routine safety laboratory, and electrocardiogram.
To evaluate and compare patient reported health-related quality of life (QoL) in terms of EORTC QLQ-C30 scores and single questions on burden by side-effects and time spent on treatment in patients treated with ribociclib plus aromatase inhibitor (AI)/fulvestrant OR chemotherapy (capecitabine plus bevacizumab OR paclitaxel with or without bevacizumab) in the first-line setting.</td></tr>
<tr><td colspan="4">Methodology:
RIBBIT was a prospective, randomized, open-label, multicenter, two-arm, phase III study.</td></tr>
<tr><td>Number of patients:
Planned (randomized): N=158
Enrolled: N=41

During the study the recruitment rate was persistently and considerably lower than originally expected. In addition, the experimental treatment used in the RIBBIT study evolved to be frequently used in routine clinical practice, thus, the primary scientific question of the study was no longer valid. Therefore, the sponsor decided</td><td>Randomized:
Total: N=38

Arm A (N=19):
Ribociclib + AI / fulvestrant

Arm B (N=19):
Paclitaxel +/- bevacizumab OR capecitabine + bevacizumab</td><td colspan="2">Analyzed:
<u>Efficacy:</u> intention-to-treat (ITT)
Arm A: N=19
Arm B: N=19

<u>Safety:</u> safety set (SAF)
Arm A: N=18
Arm B: N=18

<u>Quality of life:</u> QoL set (QOL)
Arm A: N=16
Arm B: N=16</td></tr>
</table>

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to end the recruitment prematurely. Screening failures detected after randomization were not replaced.		

Diagnosis and main criteria for inclusion:

Eligible patients were aged ≥18 years, female (any menopausal state), diagnosed with metastatic HR-positive, HER2-negative BC, presented with visceral metastases, had ECOG performance status 0-1, had not received any prior palliative systemic antineoplastic therapy for advanced disease, and were eligible for palliative treatment with ribociclib + AI / fulvestrant OR capecitabine plus bevacizumab OR paclitaxel with or without bevacizumab according to the respective summary of product characteristics (SmPCs). All inclusion and exclusion criteria are detailed in sections 9.3.1 and 9.3.2.

Test product, dose and mode of administration, batch number (arm A):

Ribociclib (LEE011, Kisqali®; 600 mg/day orally on days 1 to 21 of a 28-day cycle) + AI (once a day orally on a continuous daily schedule – days 1 to 28 of a 28-day cycle; letrozole (2.5 mg/day) or anastrozole (1 mg/day) or exemestane (25 mg/day)) or fulvestrant (intramuscular administration; 500 mg/application on days 1, 15 and 29 in cycle 1 and thereafter once per a 28-day cycle).

The selection of endocrine combination partner was at the discretion of respective treating physician. If patients had received adjuvant AI treatment, it was recommended to combine ribociclib with a steroidal AI if a non-steroidal AI had been given in the adjuvant setting and *vice versa*. Alternatively, it was recommended to combine ribociclib with fulvestrant.

Batch number: Not applicable (all study medication used was prescribed medication, i.e., commercially available).

Duration of treatment (arm A and arm B):

Patients were treated until progressive disease (PD), intolerable toxicity, withdrawal of informed consent, or death. Treatment could be continued beyond Response Evaluation Criteria in Solid Tumors (RECIST)-defined PD in case of negligible or clinically irrelevant disease progression according to the local investigator's discretion until clinically relevant disease progression or symptomatic deterioration.

Important note:

Arm A: Ribociclib must be administered in combination with an endocrine partner (AI or fulvestrant). In case of permanent discontinuation of AI / fulvestrant, ribociclib treatment had to be withdrawn. Endocrine treatment with AI or fulvestrant could be continued after discontinuation of ribociclib. Discontinuation of ribociclib and AI / fulvestrant treatment (or AI / fulvestrant if ribociclib had been discontinued earlier) was defined as end of treatment (EOT).

Arm B: Therapy with bevacizumab could be continued after discontinuation of capecitabine / paclitaxel. If treatment had been delayed for more than 1 cycle (capecitabine: 21-day cycle; paclitaxel: 28-day cycle), chemotherapy had to be discontinued. EOT was defined as discontinuation of both capecitabine / paclitaxel and bevacizumab. In case one of the two drugs had been discontinued earlier than the other, discontinuation of the second drug defined EOT.

Reference therapy, dose and mode of administration, batch number (arm B):

Capecitabine (1000 mg/m^2 orally twice daily on days 1 to 14 of a 21-day cycle) plus bevacizumab (15 mg/kg intravenously on day 1 of a 21-day cycle) OR paclitaxel (90 mg/m^2 intravenously on days 1, 8 and 15 of a 28-day cycle) with or without bevacizumab (10 mg/kg intravenously on days 1 and 15 of a 28-day cycle).

Application of paclitaxel as monotherapy or in combination with bevacizumab OR capecitabine in combination with bevacizumab was at the discretion of respective treating physician.
Important note: Maintenance treatment with any other substance including ET in patients without PD was not permitted.

Batch number: Not applicable (all study medication used was prescribed medication, i.e., commercially available).

Criteria for evaluation:

Efficacy

- The primary efficacy endpoint of this study was PFS defined as the time from randomization to PD or date of death due to any cause, whichever came first. Disease progression was assessed by imaging-based measures by the local investigator according to RECIST v1.1 until EOT due to (symptomatic) PD. In case of EOT due to other reason than PD, imaging assessments continued until PD or start of next-line therapy, whichever came first.
- Secondary efficacy endpoints included:
  - Overall response rate (ORR; complete or partial response (CR/PR)), defined as the best response achieved during first-line treatment
  - CBR (CR, PR, or stable disease lasting for 24 weeks or longer)

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- TTR defined as the time from randomization to first occurrence of any response (CR/PR)
- OS defined as the time from randomization to date of death due to any cause

Important note: Response evaluation was performed and assessed by the local investigator as per RECIST v1.1.

Safety and tolerability

- (S)AEs until 30 days after EOT: frequency, severity according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03, coding according to Medical Dictionary for Regulatory Activities (MedDRA)
- Time to deterioration of ECOG performance status from baseline (value ≤1) to a value of ≥2
- Routine safety laboratory until EOT (by-patient listing)
- Electrocardiogram (QTc time) until EOT (by-patient listing)

Patient-reported outcome (PRO): QoL (EORTC QLQ-C30)

- QoL over time and change from baseline in the global health scale and all functional and symptom scores
- Burden by side-effects of treatment at all questionnaire time points (single item)
- Burden by time spent on treatment at all questionnaire time points (four single items)

Important note: PRO assessment was initially planned to last for 36 months (every 12 weeks) after randomization or until 6 months after EOT, whichever came later. Due to the earlier termination of the study than initially planned, all data collection, including PROs, was ceased after the end of the safety follow-up period of the last patient, i.e., last-patient-last-visit (11 months after last patient enrolled).

Statistical methods:

The statistical analyses performed are detailed in the statistical analysis plan v1.0 (dated 6-Sep-2021) provided in Appendix 16.1.9 (refer to section 16. Appendices).

Determination of sample size

The sample size was calculated using PASS sample size software v14.0.9. The primary aim of the study was to examine whether the PFS is longer in arm A than in arm B.

- Null hypothesis: PFS does not differ between the two treatment arms
- Alternative hypothesis: PFS in arm A is different from PFS in arm B

For α=0.05 and 80% power, the required patient number in the RIBBIT study was 158 (79 patients per treatment arm).

Due to the low recruitment rate and the evolving of frequent use of the experimental treatment used in the RIBBIT study in routine clinical practice, the recruitment was ended prematurely following enrollment of 41 patients (38 randomized patients). With a sample size of 41 patients, the actual power achieved was 30.9%.

Analysis populations

Intention-to-treat (ITT)

- The ITT comprised all patients to whom study treatment had been assigned by randomization. According to the ITT principle, patients were analyzed according to the treatment they had been assigned to during the randomization procedure. The ITT was the relevant population for all analyses but safety, exposure, and QoL analyses.

Safety set (SAF)

- The SAF included all patients who had received at least one dose of study medication. Patients were analyzed according to the study treatment (regimen) they actually had received irrespective of the arm they had been randomized to. The SAF was the relevant analysis population for the analysis of safety and tolerability as well as exposure data.

Quality of life (QOL)

- The QOL comprised the subset of patients of the ITT for whom a baseline questionnaire was available (at least one item answered). The QOL was the relevant analysis population for all PRO analyses.

Main statistical methods

Time-to-event endpoints (PFS, OS) were estimated by using the Kaplan-Meier (KM) method. PFS/OS in the two treatment arms was compared using a stratified two-sided log-rank test at a significance level of 5%. Stratification was done according to the strata used in the randomization process. Hazard ratios (HRs) for PFS and OS with 95% confidence interval (CI) were estimated based on Cox's proportional hazard model. Response rates were evaluated based on the best tumor response documented as assessed by the local investigator according to RECIST v1.1. Patients with only non-

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measurable disease at baseline were considered responders in case a CR had been achieved. All other patients without measurable disease were considered non-responders. Rates are reported with exact binomial 95% CI according to the Clopper-Pearson method. Time to deterioration of ECOG performance status was estimated by using the KM method. All scales of the EORTC QLQ-C30 questionnaire were calculated according to the respective manual.
The remaining efficacy and safety variables were evaluated using descriptive statistics and frequency distributions.

SUMMARY – OVERALL CONCLUSIONS:

After about 3.5 years of study conduct, the RIBBIT study was terminated on 30-Nov-2021. During this time, 41 patients were enrolled (12 study sites), of whom 38 patients were randomized 1:1 to either study arm. This study did not recruit the number of patients as originally planned (178 randomized patients). Indeed, the recruitment rate was persistently and considerably lower than originally anticipated. In addition, there was a change in the therapeutic landscape since the beginning of this study as the experimental treatment (arm A) used in the RIBBIT study evolved to be frequently used in routine clinical practice. Hence, the primary scientific question of the study was no longer valid, i.e., whether to choose ribociclib plus ET or a chemotherapy-based treatment strategy in the first-line setting for patients with HR-positive, HER2-negative advanced BC. Therefore, the sponsor decided to end the recruitment prematurely, which in the end lasted for about 2.5 years following enrollment of the first patient, reflecting the conspicuously low patient accrual. This decision required a substantial protocol amendment (amendment 5), in which also the date of study termination was pushed forward. Indeed, the main reason for end of study was “study terminated by sponsor” in both study arms (>60% of patients).

The reason for slower recruitment than originally expected is not clear. It cannot be ruled out that the COVID-19 pandemic has had a negative impact on the recruitment. Importantly, the COVID-19 pandemic may also have had a direct impact on the primary endpoint of the study (i.e., PFS). Tumor assessment pertains to the PFS. For a relatively high proportion of patients, tumor assessments were either not performed or delayed at most pre-defined timepoints, and therefore not performed as scheduled, i.e., a protocol deviation (PDV). Although not all PDVs were tagged as such, one may not leave out the COVID-19 pandemic as a plausible cause for some or even all the PDVs related to delayed tumor assessment (15% of all PDVs). Delayed tumor assessment poses a risk of bias for PFS.

In total, 19 patients in each arm were included in the final analysis with a median observation time of 24.4 months in arm A and 18.2 months in arm B. Median age was 60 years and 68 years in arm A and arm B, respectively, which reflects the average age for this disease and disease stage. Most patients (89.5%) in both study arms had received concomitant medication, as presumed for this age group.

Due to the considerably fewer patients included than originally planned, the analyses of the study endpoints were greatly limited, particularly concerning the analysis of the primary endpoint. The markedly reduced numbers of patients and study sites greatly limit the significance of the efficacy and safety data, and the conclusions that can be drawn.

EFFICACY RESULTS

PRIMARY ENDPOINT – Progression-Free Survival

No evidence for a difference in PFS between study arms was found (*Table 1*).

Table 1. Primary endpoint – Progression-free survival [months] (ITT)

Kaplan-Meier statistics	Arm A (N=19)	Arm B (N=19)
Patients, n	19	19
Events, n (%)	8 (42.1%)	6 (31.6%)
Median [95% CI]	27.3 [19.1, NA]	15.8 [8.2, NA]
6-month rate [95% CI]	76.5% [58.7, 99.5]	80.2% [62.2, 100.0]
12-month rate [95% CI]	70.1% [51.2, 96.0]	62.4% [40.5, 96.1]
18-month rate [95% CI]	70.1% [51.2, 96.0]	41.6% [16.7, 100.0]
Hazard ratio arm A vs. arm B [95% CI]		0.86 [0.29, 2.60]
Log-rank test, *p*-value		0.793

CI = Confidence Interval; ITT = Intention-to Treat Set; N/n = Number; NA = Not Available*
*Parameter not estimable.
PFS was defined as the time from randomization to PD or date of death due to any cause, whichever came first. The hazard ratio between study arms was estimated employing univariable Cox regression. PFS in the two treatment arms was compared using a stratified two-sided log-rank test.

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SECONDARY ENDPOINTS

Tumor Response

The ORR and CBR were comparable between study arms (*Table 2*).

Table 2. Tumor response (ITT)

	Arm A (N=19)	Arm B (N=19)
Best overall response, n (%)		
CR	2 (10.5%)	0
PR	9 (47.4%)	11 (57.9%)
SD	4 (21.1%)	4 (21.1%)
Non-CR/Non-PD[1]	0	0
PD	3 (15.8%)	2 (10.5%)
NE	0	0
Unknown	1 (5.3%)	2 (10.5%)
Overall response rate[2], n (%) [95% CI]		
	11 (57.9%) [33.5, 79.7]	10 (52.6%) [28.9, 75.6]
Clinical benefit rate[3], n (%) [95% CI]		
	12 (63.2%) [38.4, 83.7]	14 (73.7%) [48.8, 90.9]

CI = Confidence Interval; CR = Complete Response; ITT = Intention-to Treat Set; N/n = Number; NE = Not Evaluable; PD = Progressive Disease; PR = Partial Response; SD = Stable Disease
[1]Clinical tumor assessments only. [2]Arm B: one patient had only non-measurable disease and was therefore not included in the ORR calculation. [3]In arm A, 3 patients had SD <24 weeks and in arm B, one patient was documented with disease not evaluable (NE) at week 12. These patients were therefore not included in the CBR calculation.

Time to Response

The median TTR (i.e., CR or PR) was similar between study arms (*Table 3*).

Table 3. Time to tumor response (CR/PR) [weeks] (ITT)

	Arm A (N=19)	Arm B (N=19)
n[1]	11	10
Median	13.57	12.64
Min–Max	11.9 – 71.6	11.9 – 19.7

CR = Complete Response; ITT = Intention-to Treat Set; Max = Maximum; Min = Minimum; N/n = Number; PR = Partial Response
[1]One patient in arm B had only non-measurable disease and was therefore excluded from the analysis.

Overall Survival

No evidence for a difference in OS between study arms was found (*Table 4*).

Table 4. Overall survival [months] (ITT)

Kaplan-Meier statistics	Arm A (N=19)	Arm B (N=19)
Patients, n	19	19
Events, n (%)	2 (10.5%)	5 (26.3%)
Median [95% CI]	NA [27.3, NA]	28.4 [25.0, NA]
Hazard ratio arm A vs. arm B [95% CI]		0.35 [0.07, 1.80]
Log-rank test, *p*-value		0.186

CI = Confidence Interval; ITT = Intention-to Treat Set; N/n = Number; NA = Not Available*
*Parameter not estimable.
OS was defined as the time from randomization to date of death due to any cause. The hazard ratio between study arms was estimated employing univariable Cox regression. OS in the two treatment arms was compared using a stratified two-sided log-rank test.

Patient-Reported Outcome (QOL)

The validated cancer-specific questionnaire EORTC QLQ-C30 (v3.0) and additional items (burden by side-effects / time spent on treatment – response scales: *"not at all"*, *"a little"*, *"quite a bit"*, *"very much"*) were used for evaluation of patient-reported QoL (at baseline prior to start of study treatment, every 12 weeks thereafter, and at PD).

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EORTC QLQ-C30 – Global Health Status, Physical Functioning, and Emotional Functioning

Overall, comparable scores between study arms were observed at baseline prior to start of treatment, over time*, and at radiologically confirmed PD with a slight tendency towards better QoL in arm A. In both study arms, scores were lower at PD as compared to baseline.

Burden By Side-Effects / Time Spent on Treatment

The proportion of patients, who had answered *"very much"* or *"quite a bit"* under treatment* and at PD was higher in arm B.

*Only timepoints with ≥5 evaluable questionnaires per arm considered, i.e., every 3 months up to and including the timepoint at 12 months.

SAFETY RESULTS

Extent of Exposure

The median [min – max] relative dose intensity of ribociclib, capecitabine, and paclitaxel was 95.0% [62 – 106], 72.6% [25 – 115], and 89.1% [62 – 99], respectively. The median relative dose intensity of each combination drug used was >99% in both study arms. Overall, the median [min – max] treatment duration was longer in arm A (17.0 months [3 – 34]) as compared to arm B (6.5 months [0 – 39]). The proportion of patients with a treatment modification was higher in arm B (n=16; 88.9%) as compared to arm A (n=13; 72.2%).

Treatment-Emergent Adverse Events

All but one patient (arm B) experienced a treatment-emergent AE (TEAE) during the study (*Table 5*). Overall, the number of cases was markedly higher in arm A as compared to arm B (201 vs. 140 cases), though, a smaller difference between arms was noted in terms of number of TEAEs related to study medication (100 vs. 90 cases). With regards to serious TEAEs related to study medication, the frequency of events/cases was identical between study arms (1 patient, 2 cases in each arm). TEAEs leading to discontinuation of study treatment were more common in arm B (regardless of causality). In arm B, no fatal TEAE was reported, while in arm A, one fatal event (preferred term: death) occurred, assessed as not attributable to study medication.

Table 5. Summary of TEAEs (SAF)

	Arm A (N=18)	Arm B (N=18)
All TEAEs, n (%) [cases]		
Any TEAE	18 (100%) [201]	17 (94.4%) [140]
TEAE related to study medication	15 (83.3%) [100]	16 (88.9%) [90]
Serious TEAE, n (%) [cases]		
Any serious TEAE	5 (27.8%) [9]	2 (11.1%) [3]
Serious TEAE related to study medication	1 (5.6%) [2]	1 (5.6%) [2]
TEAE of CTACE grade 3, n (%) [cases]		
Any TEAE of grade 3	11 (61.1%) [28]	9 (50%) [16]
Grade 3 TEAE related to study medication	8 (44.4%) [20]	9 (50%) [16]
TEAE of CTCAE grade 4, n (%) [cases]		
Any TEAE grade 4	2 (11.1%) [2]	1 (5.6%) [1]
Grade 4 TEAE related to study medication	2 (11.1%) [2]	1 (5.6%) [1]
TEAE leading to discontinuation of study treatment, n (%) [cases]		
Any TEAE leading to treatment discontinuation	3 (16.7%) [4]	8 (44.4%) [13]
Study medication-related TEAE leading to treatment discontinuation	2 (11.1%) [2]	7 (38.9%) [11]
Fatal TEAE, n (%) [cases]		
Any fatal TEAE	1 (5.6%) [1]	0
Fatal TEAE related to study medication	0	

CTCAE = Common Terminology Criteria for Adverse Events; N/n = Number; SAF = Safety Set; TEAE = Treatment-Emergent Adverse Event
Displayed are TEAEs defined as AEs having emerged or worsened in the *on-treatment period*, i.e., from day of first dose of study medication to 30 days after last dose of study medication. An AE was classified as related to study medication (attributable to at least one of the drugs used in the combination therapy) if the causal relationship had been classified as "suspected relationship" by the investigator or if the description of the causal relationship was missing.

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The study medication-related TEAEs reported in respective study arm are among those events expected in terms of the known safety profiles of the study drugs. The most frequent (n≥4 patients) events are detailed in *Table 6*.

Table 6. Most frequent TEAEs related to study medication (n≥4 patients) – Preferred terms (SAF)

MedDRA PT[1]	Arm A (N=18)	Arm B (N=18)
TEAE related to study medication (n≥4 patients in either arm), n (%) [cases]		
Any event	*15 (83.3%) [100]*	*16 (88.9%) [90]*
Neutropenia	9 (50.0%) [34]	4 (22.2%) [6]
Diarrhoea	1 (5.6%) [1]	6 (33.3%) [6]
Palmar-plantar erythrodysaesthesia syndrome	0	6 (33.3%) [6]
Alopecia	5 (27.8%) [5]	1 (5.6%) [1]
Hypertension	1 (5.6%) [1]	5 (27.8%) [5]
Nausea	5 (27.8%) [6]	4 (22.2%) [4]
Fatigue	1 (5.6%) [1]	4 (22.2%) [4]

MedDRA = Medical Dictionary for Regulatory Activities; N/n = Number; PT = Preferred Term; SAF = Safety Set; TEAE = Treatment-Emergent Adverse Event
[1]MedDRA v21.0 (English version).

Time to deterioration of ECOG performance status

The KM-estimated median [95% CI] TTD of ECOG performance status was not reached in arm A, while in arm B the estimated median TTD was 21.5 months [14.4, not estimable].

OVERALL CONCLUSIONS

Patient accrual did not meet expectations and the primary scientific question of the study was no longer valid following a change in the therapeutic landscape, which led to premature end of recruitment and an earlier termination of the RIBBIT study than originally planned.

Efficacy, safety, and health-related QoL were similar between study arms with a slight tendency towards a more favorable outcome in arm A, i.e., treatment of patients with HR-positive, HER2-negative MBC with CDK4/6 inhibitor in combination with ET. No new safety signals were observed.

The markedly reduced numbers of patients and study sites greatly limit the significance of the study results. Though, the results do not speak against current treatment options already established for this population in routine clinical practice.

Version and date of report: Final v1.0, 22-Aug-2022.

2.1. List of Protocol Amendments

Table 2-1 Amendments made to the protocol[1]

Protocol/amendment	Type of amendment	Changes implemented	Protocol version (Date)	Favorable opinion of the central ethics committee (Date)	Approval by the relevant competent authority (Date)
Initial study protocol	*NA*	*NA*	*V2.0 (11-Jan-2018)*	*14-Feb-2018*	*5-Feb-2018*
Amendment 1	Substantial	Amendment to the study protocol; Addition of combination partner fulvestrant (arm A). Addition of chemotherapy combination (capecitabine + bevacizumab) in arm B. Change in patient collective: Addition of premenopausal women. Change of number of patients was statistically recalculated to reach primary endpoint (sample size calculation).	v4.0 (11-Apr-2019)	4-Jun-2019	14-May-2019
Amendment 2	Non-substantial	Amendment to the study protocol; Change of exclusion criteria No. 3.	v4.1 (22-Nov-2019)	NA	NA
Amendment 3	Non-substantial	Amendment to the study protocol; Deletion of exclusion criteria No. 3 and 4.	v4.2 (18-Dec-2019)	NA	NA
Amendment 4	Substantial	Amendment to the study protocol; Changes made to SmPCs of different IMPs were added to the protocol.	v5.0 (28-Feb-2020)	16-Apr-2020	2-Apr-2020

Protocol/amendment	Type of amendment	Changes implemented	Protocol version (Date)	Favorable opinion of the central ethics committee (Date)	Approval by the relevant competent authority (Date)
Amendment 5	Substantial	Amendment to the study protocol; Premature end of recruitment and change of timelines for study termination.	v6.0 (17-Jun-2021)	2-Aug-2021	26-Jul-2021

IMP = Investigational Medicinal Product; NA = Not Applicable; SmPC = Summary of Product Characteristics
[1]The initial clinical study protocol and all its amendments were reviewed and approved by the ethical committees (ECs) and relevant competent authorities as required. All favorable opinions of the leading ECs and approvals by the relevant competent authorities are available in the Trial Master File.

2.2. List of Study Sites

Table 2-2 List of participating study sites (N=33)[1]

Center Name	Department	Street Name	Zip Code	City
Decker Ravensburg	Studienzentrum Onkologie Ravensburg Prof. Dr. Dechow, Prof. Dr. Decker, Dr. Nonnenbroich GbR	Elisabethenstraße 19	88212	Ravensburg
Otremba Oldenburg	Onkologische Praxis Oldenburg	Grüne Str. 2	26121	Oldenburg
Fuxius Heidelberg	Onkologische Schwerpunktpraxis	Kurfürsten-Anlage 34	69115	Heidelberg
Frühauf Stade	MVZ Klinik Dr. Hancken GmbH, Hämatologie und Onkologie	Harsefelder Str. 8	21680	Stade
Depenbusch Gütersloh	Onkologische Schwerpunktpraxis	Brunnenstraße 14	33332	Gütersloh
Fietz Singen (Hohentwiel)	Schwerpunktpraxis für Hämatologie und Internistische Onkologie, Gastroenterologie	Virchowstraße 10C	78224	Singen (Hohentwiel)
Reichert Westerstede	Gemeinschaftspraxis für Hämatologie und Onkologie	Kuhlenstraße 53 D	26655	Westerstede
Zahn Goslar	ÜBAG MVZ Onkologische Kooperation	Kösliner Str. 14	38642	Goslar
Jacobasch Dresden	BAG / Onkologische Gemeinschaftspraxis	Arnoldstraße 18	01307	Dresden
Hansen Kaiserslautern	IDGGQ GbR	Schneiderstraße 12	67655	Kaiserslautern
Schröder Mülheim a.d.R.	MVZ für Hämatologie und Onkologie	Kettwiger Str. 62	45468	Mülheim a.d.R.
Kurbacher Bonn	Gynäkologisches Zentrum Bonn PD Dr. med. Christian Kurbacher	Friedenspl. 16	53111	Bonn
Wolff Hamburg	OncoResearch Lerchenfeld GmbH	Lerchenfeld 14	22081	Hamburg
Welt Essen	Universitätsklinikum Essen, Frauenheilkunde und Geburtshilfe	Hufelandstraße 55	45147	Essen
Liersch Münster	GEHO - Dres. Lerchenmüller, Kratz-Albers,Timmer, Bieker & Liersch	Steinfurter Str. 60b	48149	Münster
Hagen Dortmund	St.-Johannes-Hospital, Innere Medizin II	Johannesstraße 9-13	44137	Dortmund
Welslau Aschaffenburg	MVZ am Klinikum Aschaffenburg GmbH	Am Hasenkopf 1	63739	Aschaffenburg
Graf La Rosée Villingen-Schwenningen	Schwarzwald-Baar Klinikum, Klinik für Innere Medizin I	Klinikstraße 11	78052	Villingen-Schwenningen
Stickeler Aachen	Uniklinik RWTH Aachen Gynäkologie und Geburtsmedizin	Pauwelsstraße 30	52074	Aachen
Zaiss Freiburg i.Br.	Praxis für interdisziplinäre Onkologie & Hämatologie	Wirthstraße 11c	79110	Freiburg i.Br.
Scholz Neumarkt i.d.OPf.	Klinikum Neumarkt Frauenklinik	Nürnberger Str. 12	92318	Neumarkt i.d.Opf.
Behringer Speyer	Onkologische Schwerpunktpraxis Speyer	Hilgardstraße 30	67346	Speyer
Petersen Heidenheim a.d.B.	Onkologische Schwerpunktpraxis Dr. med. Volker Petersen	Kurze Str. 5	89522	Heidenheim a.d.B.
Behlendorf Halle (Saale)	Gemeinschaftspraxis für Innere Medizin, Hämatologie, Onkologie, Gastroenterologie	Niemeyerstraße 22	06110	Halle (Saale)

Center Name	Department	Street Name	Zip Code	City
Uhlig Naunhof	Praxis Dr. med. Jens Uhlig	Schulstraße 1	04683	Naundorf
Hahn Baden-Baden	Klinikum Mittelbaden Baden-Baden Balg, Frauenheilkunde und Geburtshilfe	Balger Str. 50	76532	Baden-Baden
Stiegler Rötha	Tumorzentrum und Hausarztpraxis Rötha Leipziger-Land	August-Bebel-Straße 51	04571	Rötha
Faust Nürtingen	medius KLINIK NÜRTINGEN, Frauenheilkunde und Geburtshilfe	Auf dem Säer 1	72622	Nürtingen
Peuser Leipzig	Praxis Dr. med. Bettina Peuser	Georg-Schwarz-Straße 53	04179	Leipzig
Pelz Offenburg	Onkologie Offenburg Ambulantes Therapiezentrum für Hämatologie und Onkologie	Ebertpl. 12	77654	Offenburg
Hielscher Stralsund	Gynäkologie Kompetenzzentrum Praxis Dr. med. Carsten Hielscher	Große Parower Str. 47-53	18435	Stralsund
Emde Recklinghausen	Praxis und Tagesklinik für Onkologie und Hämatologie	Am Stadion 9	45659	Recklinghausen
Söling Kassel	Hämato-Onkologisches Zentrum Kassel GmbH	Goethestraße 47	34119	Kassel

[1]Listed are all participating study sites, i.e., all initiated and activated sites (non-recruiting and recruiting).