Clinical trial results:
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

Summary

EudraCT number	2017-002930-22
Trial protocol	DE
Global end of trial date	30 November 2021

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022
Summary attachment (see zip file)	RIBBIT_CSR_Synopsis (RIBBIT_CSR_Synopse.pdf)

Trial information

Trial identification

Sponsor protocol code	IOM-050371

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03462251
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	iOMEDICO AG
Sponsor organisation address	Ellen-Gottlieb-Str. 19, Freiburg, Germany, 79106
Public contact	Dr. Beate Niemeier, iOMEDICO AG, +49 761152420, info@iomedico.com
Scientific contact	Dr. Beate Niemeier, iOMEDICO AG, 7611524213 761152420, info@iomedico.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 January 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 November 2021
Global end of trial reached?	Yes
Global end of trial date	30 November 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy in terms of progression free survival (PFS) of ribociclib plus endocrine therapy with capecitabine with bevacizumab or paclitaxel with or without bevacizumab as first-line treatment of adult women with HR-positive, HER2-negative advanced breast cancer presenting with visceral metastasis.

Protection of trial subjects:

The study was planned, conducted and analyzed according to the protocol and in accordance with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP)-guidelines "Note for Good Clinical Practice" (CPMP/ICH/135/95) based on the principles laid down in the Declaration of Helsinki (1964) and its amendments. The Informed Consent Form was approved by the Ethics Committee. Informed consent (signed ICF) was obtained from each patient by the investigator prior to inclusion of the patient into the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 May 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 38
Worldwide total number of subjects	38
EEA total number of subjects	38

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	21
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening of patients was done by principal investigator of respective site. All patients willing to participate and expected to fulfill the in/exclusion were cosidered to be included in the trial. In total, 41 patients signed the informed consent form and were enrolled into the study (randomized: 38 / screening failures: 3)

Pre-assignment period milestones

Number of subjects started	38
Number of subjects completed	38

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

combination of ribociclib and AI / fulvestrant

Arm type	Experimental
Investigational medicinal product name	Kisqali
Investigational medicinal product code	EU/1/17/1221/001-012
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Ocular use

Dosage and administration details:

600 mg/day, day 1-21 in a 28-day cycle

Investigational medicinal product name	Anastrozole
Investigational medicinal product code	SUB05502MIG
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 mg/day

Investigational medicinal product name	Letrozole
Investigational medicinal product code	SUB08444MIG
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2.5 mg/day

Investigational medicinal product name	Exemestane
Investigational medicinal product code	SUB07492MIG
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg/day

Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	SUB13933MIG
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

500 mg/application – administration on day 1, day 15 and day 29 in cycle 1 and once per cycle thereafter

Arm title	Arm B

Arm description:

capecitabine + bevacizumab or paclitaxel +/- bevacizumab

Arm type	Active comparator
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	SUB09583MIG
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

90 mg/m2 on day 1, 8 and 15 of a 28-day cycle

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	SUB12474MIG
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

twice daily 1000 mg/m2 day 1-14 in a 21-day cycle

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	SUB16402MIG
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

In combination with Paclitaxel: 10 mg/kg on day 1 and day 15 of a 28-day cycle
In combination with Capecitabine: 15 mg/kg on day 1 of a 21-day cycle

Number of subjects in period 1	Arm A	Arm B
Started	19	19
Completed	13	12
Not completed	6	7
Consent withdrawn by subject	-	1
Death	2	5

Non-compliance	1	-
Other reason	3	1

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description: combination of ribociclib and AI / fulvestrant	
Reporting group title	Arm B
Reporting group description: capecitabine + bevacizumab or paclitaxel +/- bevacizumab	

Reporting group values	Arm A	Arm B	Total
Number of subjects	19	19	38
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	14	7	21
From 65-84 years	5	12	17
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	19	19	38
Male	0	0	0

End points

End points reporting groups

Reporting group title	Arm A
Reporting group description: combination of ribociclib and AI / fulvestrant	
Reporting group title	Arm B
Reporting group description: capecitabine + bevacizumab or paclitaxel +/- bevacizumab	

Primary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)

End point description:

The primary endpoint of this study is to compare the two treatment arms with respect to PFS. It will be assessed by imaging until EOT due to (symptomatic) progressive disease or start of next-line therapy. The evaluation of disease progression is performed by the local investigator according to RECIST v1.1 criteria (Eisenhauer et al. 2009)

95% CI upper values marked as N/A in the statistical analysis were set to "999" due to data base entry requirements

End point type	Primary

End point timeframe:

PFS is defined as time from randomization to progression of disease or death of any cause, whichever comes first.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: months				
median (confidence interval 95%)	27.3 (19.1 to 999)	15.8 (8.2 to 999)		

Statistical analyses

Statistical analysis title	PFS log-rank test

Statistical analysis description:

PFS in the two treatment arms will be compared using a stratified two-sided log-rank test at a significance level of 5%. Stratification will be done according to the strata used in the randomization process.

Comparison groups	Arm A v Arm B

Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 5
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	2.6
Variability estimate	Standard deviation

Secondary: Overall response rate (ORR)

End point title	Overall response rate (ORR)

End point description:

ORR defined as the frequency of patients in whom any response (CR/PR) could be achieved. Patients with only non-measurable disease at baseline were considered responders in case a CR had been achieved. All other patients without measurable disease were considered non-responders.
Arm B: one patient had only non-measurable disease and was therefore not included in the ORR calculation.

End point type	Secondary

End point timeframe:

Overall response rate (ORR; complete or partial response (CR/PR)), defined as the best response achieved during first-line treatment

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: Patients				
Complete Response (CR)	2	0		
Partial Response (PR)	9	11		
Stable Disease (SD)	4	4		
Non-CR/Non-PD	0	0		
Progressive Disease (PD)	3	2		
Not Evaluable (NE)	0	0		
Unknown	1	2		
ORR Responder	11	10		
ORR Non-Responder	8	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR)

End point title	Clinical Benefit Rate (CBR)

End point description:

CBR defined as the frequency of patients in whom CR, PR, or SD lasting for 24 weeks or more was achieved. Patients with only non-measurable disease at baseline were included in the numerator if they had achieved a CR as best response or a response in the category of "non-CR/non-PD".

End point type	Secondary

End point timeframe:

Complete or partial response or stable disease lasting 24 weeks or more

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: Patients				
Responder	12	14		
Non-Responder	7	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Tumor Response (TTR)

End point title	Time to Tumor Response (TTR)

End point description:

TTR will be calculated using Kaplan-Meier method. It is defined as time from randomization to first occurrence of any response (in case of measurable disease: CR or PR, assessed by local investigator according to RECIST v1.1; in case of only non-measurable disease: CR).

End point type	Secondary

End point timeframe:

TTR defined as the time from randomization to first occurrence of any response (CR/PR)

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: week				
median (full range (min-max))	13.57 (11.9 to 71.6)	12.64 (11.9 to 19.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

OS will be calculated using Kaplan-Meier method. For patients alive at individual end of study the time will be censored at date of last contact. The frequency of events and the quartiles together with 95% confidence limits according to (Klein & Moeschberger, 1997) will be presented for each arm.

95% CI upper values marked as N/A as well as median values marked as N/A in the statistical analysis were set to "999" due to data base entry requirements

End point type	Secondary

End point timeframe:

OS was defined as the time from randomization to date of death due to any cause

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: month				
median (confidence interval 95%)	999 (27.3 to 999)	28.4 (25.0 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: EORTC QLQC30 global health status

End point title	EORTC QLQC30 global health status

End point description:

The EORTC QLQ-C30 questionnaire provides five functional scales, three symptom scales two global items and several single items. Each item is answered with “not at all”, “a little”, “quite a bit” and “very much”, rated as 1 (not at all), 2, 3 or 4 (very much). Higher scores indicate better QoL.
Missing data were set to "999" due to data base entry requirements

End point type	Secondary

End point timeframe:

At baseline prior to start of study treatment until 36 months after randomization, every 12 weeks and at radiologic disease progression.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: score value (0 - 100)				
median (full range (min-max))				
Baseline	50.0 (17 to 92)	54.2 (4 to 92)		
Week 12	66.7 (25 to 100)	50.0 (25 to 83)		

Week 24	50.0 (0 to 83)	50 (17 to 83)		
Week 36	66.7 (33 to 83)	62.5 (17 to 83)		
Week 48	58.3 (0 to 83)	58.3 (25 to 75)		
Week 60	58.3 (17 to 100)	50.0 (33 to 83)		
Week 72	66.7 (25 to 100)	75.0 (75 to 75)		
Week 84	66.7 (0 to 83)	33.3 (33 to 92)		
Week 96	83.3 (67 to 100)	75 (75 to 75)		
Week 108	83.3 (83 to 83.3)	91.7 (91.7 to 92)		
Week 120	83.3 (83 to 83.3)	83.3 (83 to 83.3)		
Week 132	75.0 (75 to 75)	83.3 (83 to 83.3)		
Week 144	999 (999 to 999)	83.3 (83 to 83.3)		
Progression	50.0 (17 to 67)	41.7 (33 to 67)		

Statistical analyses

No statistical analyses for this end point

Secondary: Burden by time spent on treatment

End point title	Burden by time spent on treatment

End point description:

Patients were asked a question on burden by time spent on treatment. Response scales range from 0 to 4 (“not at all”, “a little”, “quite a bit”, “very much”) with higher score representing a high burden level.

End point type	Secondary

End point timeframe:

At baseline prior to start of study treatment until 36 months after randomization, every 12 weeks and at radiologic disease progression.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: Patients				
Baseline - Not at all	4	2		
Baseline - A little	5	4		
Baseline - Quite a bit	1	0		
Baseline - Very much	0	3		
Baseline - Missing	6	7		
Week 12 - Not at all	5	2		
Week 12 - A little	4	4		
Week 12 - Quite a bit	3	9		
Week 12 - Very much	1	0		
Week 12 - Missing	1	0		
Week 24 - Not at all	3	1		

Week 24 - A little	4	4		
Week 24 - Quite a bit	3	5		
Week 24 - Very much	3	1		
Week 24 - Missing	0	0		
Week 36 - Not at all	2	2		
Week 36 - A little	3	3		
Week 36 - Quite a bit	4	2		
Week 36 - Very much	0	1		
Week 36 - Missing	0	0		
Week 48 - Not at all	5	1		
Week 48 - A little	2	1		
Week 48 - Quite a bit	1	3		
Week 48 - Very much	2	0		
Week 48 - Missing	0	0		
Week 60 - Not at all	1	1		
Week 60 - A little	2	0		
Week 60 - Quite a bit	3	3		
Week 60 - Very much	1	0		
Week 60 - Missing	1	0		
Week 72 - Not at all	1	0		
Week 72 - A little	4	1		
Week 72 - Quite a bit	1	2		
Week 72 - Very much	1	0		
Week 72 - Missing	0	0		
Week 84 - Not at all	1	0		
Week 84 - A little	1	1		
Week 84 - Quite a bit	2	2		
Week 84 - Very much	1	0		
Week 84 - Missing	1	0		
Week 96 - Not at all	1	0		
Week 96 - A little	2	0		
Week 96 - Quite a bit	1	1		
Week 96 - Very much	0	0		
Week 96 - Missing	0	0		
Week 108 - Not at all	0	0		
Week 108 - A little	1	1		
Week 108 - Quite a bit	0	0		
Week 108 - Very much	0	0		
Week 108 - Missing	0	0		
Week 120 - Not at all	0	0		
Week 120 - A little	1	1		
Week 120 - Quite a bit	0	0		
Week 120 - Very much	0	0		
Week 120 - Missing	0	0		
Week 132 - Not at all	0	0		
Week 132 - A little	0	0		
Week 132 - Quite a bit	1	1		
Week 132 - Very much	0	0		
Week 132 - Missing	0	0		
Week 144 - Not at all	0	0		
Week 144 - A little	0	1		
Week 144 - Quite a bit	0	0		

Week 144 - Very much	0	0		
Week 144 - Missing	0	0		
Progression - Not at all	1	1		
Progression - A little	4	1		
Progression - Quite a bit	2	4		
Progression - Very much	0	0		
Progression - Missing	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Burdened by side effects of treatment

End point title	Burdened by side effects of treatment

End point description:

Patients were asked a question concerning the burden caused by side effects of treatment. Response scales range from 0 to 4 (“not at all”, “a little”, “quite a bit”, “very much”) with higher score representing a high burden level.

End point type	Secondary

End point timeframe:

At baseline prior to start of study treatment until 36 months after randomization, every 12 weeks and at radiologic disease progression.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: Patients				
Baseline - Not at all	4	4		
Baseline - A little	5	2		
Baseline - Quite a bit	1	1		
Baseline - Very much	0	0		
Baseline - Missing	6	9		
Week 12 - Not at all	3	0		
Week 12 - A little	4	3		
Week 12 - Quite a bit	6	7		
Week 12 - Very much	0	5		
Week 12 - Missing	1	0		
Week 24 - Not at all	1	0		
Week 24 - A little	6	0		
Week 24 - Quite a bit	2	8		
Week 24 - Very much	3	3		
Week 24 - Missing	1	0		
Week 36 - Not at all	3	1		
Week 36 - A little	3	3		
Week 36 - Quite a bit	3	3		
Week 36 - Very much	0	1		

Week 36 - Missing	0	0		
Week 48 - Not at all	3	0		
Week 48 - A little	2	2		
Week 48 - Quite a bit	5	2		
Week 48 - Very much	0	1		
Week 48 - Missing	0	0		
Week 60 - Not at all	1	0		
Week 60 - A little	2	1		
Week 60 - Quite a bit	4	2		
Week 60 - Very much	0	1		
Week 60 - Missing	1	0		
Week 72 - Not at all	1	0		
Week 72 - A little	3	1		
Week 72 - Quite a bit	2	1		
Week 72 - Very much	0	1		
Week 72 - Missing	1	0		
Week 84 - Not at all	1	0		
Week 84 - A little	2	1		
Week 84 - Quite a bit	2	0		
Week 84 - Very much	1	2		
Week 84 - Missing	0	0		
Week 96 - Not at all	2	0		
Week 96 - A little	1	0		
Week 96 - Quite a bit	0	1		
Week 96 - Very much	0	0		
Week 96 - Missing	1	0		
Week 108 - Not at all	0	0		
Week 108 - A little	1	1		
Week 108 - Quite a bit	0	0		
Week 108 - Very much	0	0		
Week 108 - Missing	0	0		
Week 120 - Not at all	0	0		
Week 120 - A little	0	1		
Week 120 - Quite a bit	1	0		
Week 120 - Very much	0	0		
Week 120 - Missing	0	0		
Week 132 - Not at all	0	0		
Week 132 - A little	0	0		
Week 132 - Quite a bit	0	1		
Week 132 - Very much	1	0		
Week 132 - Missing	0	0		
Week 144 - Not at all	0	0		
Week 144 - A little	0	0		
Week 144 - Quite a bit	0	1		
Week 144 - Very much	0	0		
Week 144 - Missing	0	0		
Progression - Not at all	2	1		
Progression - A little	4	1		
Progression - Quite a bit	1	3		
Progression - Very much	0	1		
Progression - Missing	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to deterioration of ECOG performance status

End point title	Time to deterioration of ECOG performance status

End point description:

Time to deterioration of ECOG performance status was calculated using Kaplan-Meier method.
12-month rates [95% CI]: Arm A: 87.2% [71.9, 100.0], and Arm B: 71.2% [50.1, 100.0].
(Data provided as NA in the statistical analysis were set to "999" due to data base entry requirements.

End point type	Secondary

End point timeframe:

Time from baseline (ECOG value >= 1) to a ECOG value <= 2).

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[1]	18[2]		
Units: months				
median (confidence interval 95%)	999 (25.1 to 999)	21.5 (14.4 to 999)		

Notes:

[1] - Safety Set

[2] - Safety Set

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The adverse event reporting period starts after informed consent was signed. The reporting period includes 30 days after EOT (i.e. the day of last intake of oral study medication or the end of the last treatment cycle for intravenous study treatment)

Adverse event reporting additional description:

Every SAE, occurring after the patient has provided informed consent and until 30 days after the patient has stopped study treatment had to be reported via eCRF data entry within 24 hours of learning of its occurrence. All SAE related data entered into the eCRF were forwarded automatically to iOMEDICO pharmacovigilance for further processing.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21

Reporting groups

Reporting group title	Arm A

Reporting group description:

combination of ribociclib and AI / fulvestrant

Reporting group title	Arm B

Reporting group description:

capecitabine + bevacizumab or paclitaxel +/- bevacizumab

Serious adverse events	Arm A	Arm B	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 18 (27.78%)	2 / 18 (11.11%)	
number of deaths (all causes)	2	5	
number of deaths resulting from adverse events	1	0	
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Thrombosis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			

subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			

subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Arm A	Arm B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 18 (100.00%)	17 / 18 (94.44%)	
Vascular disorders			
Embolism arterial			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Haematoma			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Hot flush			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Hypertension			
subjects affected / exposed	2 / 18 (11.11%)	6 / 18 (33.33%)	
occurrences (all)	2	6	
Hypotension			
subjects affected / exposed	0 / 18 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	2	
Lymphoedema			

subjects affected / exposed	1 / 18 (5.56%)	2 / 18 (11.11%)	
occurrences (all)	1	2	
Phlebitis			
subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Thrombosis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Cataract operation			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Dental care			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Mastectomy			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	3 / 18 (16.67%)	6 / 18 (33.33%)	
occurrences (all)	4	6	
Gait disturbance			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
General physical health deterioration			
subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Mucosal inflammation			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Oedema peripheral			

subjects affected / exposed	2 / 18 (11.11%)	2 / 18 (11.11%)	
occurrences (all)	4	2	
Pain			
subjects affected / exposed	2 / 18 (11.11%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Lip infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	2 / 18 (11.11%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Nipple inflammation			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 18 (11.11%)	1 / 18 (5.56%)	
occurrences (all)	2	1	
Dysphonia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Dyspnoea			
subjects affected / exposed	2 / 18 (11.11%)	2 / 18 (11.11%)	
occurrences (all)	2	2	
Epistaxis			
subjects affected / exposed	0 / 18 (0.00%)	3 / 18 (16.67%)	
occurrences (all)	0	3	
Oropharyngeal pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Painful respiration			

subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Rhinitis allergic			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Throat irritation			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 18 (11.11%)	2 / 18 (11.11%)	
occurrences (all)	3	2	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 18 (5.56%)	2 / 18 (11.11%)	
occurrences (all)	1	2	
Blood bilirubin increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Haemoglobin decreased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Karnofsky scale worsened			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Neutrophil count decreased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Platelet count decreased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Weight decreased			

subjects affected / exposed	3 / 18 (16.67%)	1 / 18 (5.56%)	
occurrences (all)	3	1	
White blood cell count decreased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis radiation			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Upper limb fracture			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Arrhythmia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Cardiac failure			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Cardiovascular disorder			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Tachycardia			
subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Dysaesthesia			

subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Dysgeusia			
subjects affected / exposed	0 / 18 (0.00%)	3 / 18 (16.67%)	
occurrences (all)	0	3	
Headache			
subjects affected / exposed	2 / 18 (11.11%)	3 / 18 (16.67%)	
occurrences (all)	2	3	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Polyneuropathy			
subjects affected / exposed	0 / 18 (0.00%)	3 / 18 (16.67%)	
occurrences (all)	0	5	
Syncope			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 18 (11.11%)	1 / 18 (5.56%)	
occurrences (all)	2	1	
Iron deficiency anaemia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Leukopenia			
subjects affected / exposed	3 / 18 (16.67%)	0 / 18 (0.00%)	
occurrences (all)	4	0	
Neutropenia			
subjects affected / exposed	9 / 18 (50.00%)	4 / 18 (22.22%)	
occurrences (all)	34	6	
Thrombocytopenia			
subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Ear and labyrinth disorders			
Vertigo			

subjects affected / exposed	3 / 18 (16.67%)	3 / 18 (16.67%)	
occurrences (all)	3	4	
Eye disorders			
Eye inflammation			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Eye irritation			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Visual impairment			
subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 18 (11.11%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Abdominal pain upper			
subjects affected / exposed	2 / 18 (11.11%)	2 / 18 (11.11%)	
occurrences (all)	3	2	
Anal inflammation			
subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Constipation			
subjects affected / exposed	4 / 18 (22.22%)	1 / 18 (5.56%)	
occurrences (all)	4	1	
Diarrhoea			
subjects affected / exposed	5 / 18 (27.78%)	8 / 18 (44.44%)	
occurrences (all)	9	8	
Dry mouth			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Dysphagia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Flatulence			

subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Gastric disorder			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 18 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	2	
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	7 / 18 (38.89%)	5 / 18 (27.78%)	
occurrences (all)	8	5	
Noninfective gingivitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Oral pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Stomatitis			
subjects affected / exposed	4 / 18 (22.22%)	3 / 18 (16.67%)	
occurrences (all)	4	3	
Umbilical hernia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	2 / 18 (11.11%)	2 / 18 (11.11%)	
occurrences (all)	2	2	
Extravasation			

subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	5 / 18 (27.78%)	1 / 18 (5.56%)	
occurrences (all)	5	1	
Dermatitis contact			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Onychoclasis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 18 (0.00%)	6 / 18 (33.33%)	
occurrences (all)	0	6	
Photosensitivity reaction			
subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Pruritus			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	4 / 18 (22.22%)	0 / 18 (0.00%)	
occurrences (all)	5	0	
Rash maculo-papular			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Rash pruritic			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Toxic erythema of chemotherapy			

subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Vitiligo			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Proteinuria			
subjects affected / exposed	0 / 18 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	2	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 18 (16.67%)	2 / 18 (11.11%)	
occurrences (all)	4	3	
Back pain			
subjects affected / exposed	2 / 18 (11.11%)	0 / 18 (0.00%)	
occurrences (all)	3	0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	0	
Myalgia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Neck pain			

subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Psoriatic arthropathy			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Spinal pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	3	0	
Cardiac myxoma			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Gastroenteritis viral			
subjects affected / exposed	2 / 18 (11.11%)	1 / 18 (5.56%)	
occurrences (all)	2	1	
Gingivitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Herpes zoster			
subjects affected / exposed	1 / 18 (5.56%)	2 / 18 (11.11%)	
occurrences (all)	1	2	
Hordeolum			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Lung infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	1 / 18 (5.56%)	2 / 18 (11.11%)	
occurrences (all)	1	2	

Oral candidiasis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Oral herpes			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Periodontitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Pulpitis dental			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Respiratory tract infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Root canal infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Sinusitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	3 / 18 (16.67%)	1 / 18 (5.56%)	
occurrences (all)	7	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 18 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	2	
Diabetes mellitus			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Hyperglycaemia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Hypokalaemia			

subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 May 2019	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
02 April 2020	Amendment to the study protocol; Changes made to SmPCs of different IMPs were added to the protocol.
26 July 2021	Amendment to the study protocol; Stop of recruitment and change of study termination

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

During the recruitment phase accrual was very low hence, recruitment of patients into the RIBBIT study was stopped after the inclusion of 41 patients.

Notes: