Clinical trial results:
Anti-hormonal maintenance treatment with the CDK4/6 inhibitor Ribociclib after 1st line chemotherapy in hormone receptor positive / HER2 negative metastatic breast cancer: A phase II trial

Summary

EudraCT number	2017-003667-35
Trial protocol	DE
Global end of trial date	21 July 2022

Results information

Result version number	v1 (current)
This version publication date	04 August 2023
First version publication date	04 August 2023

Trial information

Trial identification

Sponsor protocol code	GBG-97-AMICA

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03555877
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GBG Forschungs GmbH
Sponsor organisation address	Dornhofstr. 10, Neu-Isenburg, Germany, 63263
Public contact	Publications, GBG Forschungs GmbH, +49 610274800, publications@gbg.de
Scientific contact	Publications, GBG Forschungs GmbH, +49 610274800, publications@gbg.de

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	24 March 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 July 2022
Global end of trial reached?	Yes
Global end of trial date	21 July 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To estimate the median PFS with 95% confidence interval (CI) of an anti-hormonal maintenance therapy with the CDK4/6 inhibitor ribociclib after 1st line chemotherapy at the discretion of the investigator (e.g. taxanes, capecitabine, vinorelbine, anthracycline)

Protection of trial subjects:

The trial protocol including amendments, patient information, and the informed consent were reviewed and approved from a properly constituted IRB/IEC for each site prior to the study start. The study was conducted in accordance with the Declaration of Helsinki and its revisions, the International Conference on Harmonization (ICH) - Harmonized Tripartite Guideline for Good Clinical Practice (GCP) (E6), and in accordance with applicable laws of the pertinent regulatory authorities in all aspects of preparation, monitoring, reporting, auditing, and archiving. IDMC was involved to ensure the ethical conduct of the trial and to protect patients' safety interests in this study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 February 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 53
Worldwide total number of subjects	53
EEA total number of subjects	53

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)	28

From 65 to 84 years	23
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 13 sites in Germany (between March 2018 and July 2022). A total of 70 patients were screened, of whom 53 started treatment.

Pre-assignment

Screening details:

Women with HR+/HER2- locally advanced or metastatic BC with disease control (at least stable disease) after at least 4 cycles of a mono- or polychemotherapy and no more than one previous line of ET treatment; maintenance ET could have already been started up to 6 weeks before enrolment, but after achievement of tumor response or stable disease.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ribociclib + ET

Arm description:

Ribociclib + ET (with anastrozole, letrozole, exemestane, or fulvestrant +/-LHRH-analogue for premenopausal women)

Arm type	Experimental
Investigational medicinal product name	Ribociclib
Investigational medicinal product code	
Other name	KISQALI®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ribociclib at a dose of 600 mg (3x200mg) was administered orally once a day for 21 days followed by 7 days off treatment of every 28-day cycle

Arm title	ET alone

Arm description:

ET alone (Anastrozole, Letrozole, Exemestane, or Fulvestrant).
Premenopausal patients received LHRH-analogue in addition to ET.
Note: This arm was not part of the modified intention-to-treat analysis (mITT), see Amendment 3.

Arm type	Descriptive
Investigational medicinal product name	Anastrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 mg tablets administered once per day orally

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

Dosage and administration details: 2.5 mg tablets administered once per day orally	
Investigational medicinal product name	Exemestane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 25 mg tablets administered once per day orally	
Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

prefilled syringes with fulvestrant 250mg each: 500 mg given once a month intramuscularly, with an additional 500 mg dose given two weeks after the first dose.

Number of subjects in period 1	Ribociclib + ET	ET alone
Started	43	10
Completed	12	1
Not completed	31	9
Physician decision	1	-
Adverse event, non-fatal	2	-
Death without documented progression	1	-
Lost to follow-up	1	-
Progressive disease	25	9
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Ribociclib + ET
Reporting group description:	
Ribociclib + ET (with anastrozole, letrozole, exemestane, or fulvestrant +/-LHRH-analogue for premenopausal women)	
Reporting group title	ET alone
Reporting group description:	
ET alone (Anastrozole, Letrozole, Exemestane, or Fulvestrant). Premenopausal patients received LHRH-analogue in addition to ET. Note: This arm was not part of the modified intention-to-treat analysis (mITT), see Amendment 3.	

Reporting group values	Ribociclib + ET	ET alone	Total
Number of subjects	43	10	53
Age categorical Units: Subjects			
< 40 years	1	0	1
40 - < 50 years	5	0	5
50 - < 65 years	19	3	22
65 years and above	18	7	25
Age continuous Units: years			
median	61	70	
full range (min-max)	36 to 87	50 to 85	-
Gender categorical Units: Subjects			
Female	43	10	53
Male	0	0	0

End points

End points reporting groups

Reporting group title	Ribociclib + ET

Reporting group description:

Ribociclib + ET (with anastrozole, letrozole, exemestane, or fulvestrant +/-LHRH-analogue for premenopausal women)

Reporting group title	ET alone

Reporting group description:

ET alone (Anastrozole, Letrozole, Exemestane, or Fulvestrant).
Premenopausal patients received LHRH-analogue in addition to ET.
Note: This arm was not part of the modified intention-to-treat analysis (mITT), see Amendment 3.

Primary: Progression-free survival

End point title	Progression-free survival

End point description:

Patients lost to follow-up or alive at the end of the study were censored at the date of last contact. In addition, patients starting a chemotherapy or targeted therapy after discontinuation of ET were censored at the date of the beginning of the new therapy.

End point type	Primary

End point timeframe:

Time in months between enrolment and tumor progression or death from any cause.

End point values	Ribociclib + ET	ET alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	10		
Units: month				
median (confidence interval 95%)	12.4 (8.7 to 24.4)	4.75 (1 to 10.3)		

Statistical analyses

Statistical analysis title	Kaplan – Meier method

Statistical analysis description:

The median PFS and the corresponding 95% CI as well as the PFS curve were estimated using the Kaplan – Meier method. Patients lost to follow up or those who were progression-free at the end of the study were censored at the date of last contact. Patients starting a chemotherapy or targeted therapy after discontinuation of endocrine therapy were censored at the date of the beginning of the new therapy.

Comparison groups	Ribociclib + ET v ET alone

Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 9999 [2]
Method	None
Parameter estimate	Confidence interval
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard error of the mean

Notes:

[1] - Median PFS with corresponding 95% CIs were estimated, and survival curves were plotted (estimation via Kaplan-Meier)

[2] - No p-value measured. Fields filled to avoid error.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events occurring during the study treatment period were reported.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Ribociclib + ET
Reporting group description: -	
Reporting group title	ET only

Reporting group description: -

Serious adverse events	Ribociclib + ET	ET only	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 43 (25.58%)	1 / 10 (10.00%)	
number of deaths (all causes)	14	1	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Spinal compression fracture			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	0 / 43 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			

subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Endometrial hyperplasia			

subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteonecrosis of jaw			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (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			
Pneumonia			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infection			
subjects affected / exposed	0 / 43 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device occlusion			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Ribociclib + ET	ET only	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 43 (100.00%)	10 / 10 (100.00%)	
Vascular disorders			

Embolism			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	19 / 43 (44.19%)	2 / 10 (20.00%)	
occurrences (all)	19	2	
Mucosal inflammation			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	3 / 43 (6.98%)	0 / 10 (0.00%)	
occurrences (all)	3	0	
Oedema peripheral			
subjects affected / exposed	10 / 43 (23.26%)	1 / 10 (10.00%)	
occurrences (all)	10	1	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	2 / 43 (4.65%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Reproductive system and breast disorders			
Vulvovaginal dryness			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Hot flush			
subjects affected / exposed	9 / 43 (20.93%)	2 / 10 (20.00%)	
occurrences (all)	9	2	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	3 / 43 (6.98%)	1 / 10 (10.00%)	
occurrences (all)	3	1	
Dyspnoea			
subjects affected / exposed	12 / 43 (27.91%)	1 / 10 (10.00%)	
occurrences (all)	12	1	
Cough			

subjects affected / exposed	7 / 43 (16.28%)	0 / 10 (0.00%)	
occurrences (all)	7	0	
Pleural effusion			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 43 (9.30%)	1 / 10 (10.00%)	
occurrences (all)	4	1	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	5 / 43 (11.63%)	0 / 10 (0.00%)	
occurrences (all)	5	0	
Blood alkaline phosphatase increased			
subjects affected / exposed	22 / 43 (51.16%)	4 / 10 (40.00%)	
occurrences (all)	22	4	
Aspartate aminotransferase increased			
subjects affected / exposed	26 / 43 (60.47%)	2 / 10 (20.00%)	
occurrences (all)	26	2	
Alanine aminotransferase increased			
subjects affected / exposed	25 / 43 (58.14%)	2 / 10 (20.00%)	
occurrences (all)	25	2	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Blood creatinine increased			
subjects affected / exposed	17 / 43 (39.53%)	3 / 10 (30.00%)	
occurrences (all)	17	3	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 43 (13.95%)	0 / 10 (0.00%)	
occurrences (all)	6	0	
Dysgeusia			
subjects affected / exposed	2 / 43 (4.65%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Syncope			

subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Cognitive disorder			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Nervous system disorder			
subjects affected / exposed	10 / 43 (23.26%)	2 / 10 (20.00%)	
occurrences (all)	10	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	26 / 43 (60.47%)	5 / 10 (50.00%)	
occurrences (all)	26	5	
Leukopenia			
subjects affected / exposed	41 / 43 (95.35%)	1 / 10 (10.00%)	
occurrences (all)	41	1	
Neutropenia			
subjects affected / exposed	40 / 43 (93.02%)	1 / 10 (10.00%)	
occurrences (all)	40	1	
Thrombocytopenia			
subjects affected / exposed	19 / 43 (44.19%)	3 / 10 (30.00%)	
occurrences (all)	19	3	
Febrile neutropenia			
subjects affected / exposed	2 / 43 (4.65%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	3 / 43 (6.98%)	1 / 10 (10.00%)	
occurrences (all)	3	1	
Eye disorders			
Lacrimation increased			
subjects affected / exposed	2 / 43 (4.65%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Dry eye			
subjects affected / exposed	7 / 43 (16.28%)	0 / 10 (0.00%)	
occurrences (all)	7	0	
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	22 / 43 (51.16%)	3 / 10 (30.00%)	
occurrences (all)	22	3	
Vomiting			
subjects affected / exposed	9 / 43 (20.93%)	0 / 10 (0.00%)	
occurrences (all)	9	0	
Dyspepsia			
subjects affected / exposed	7 / 43 (16.28%)	0 / 10 (0.00%)	
occurrences (all)	7	0	
Constipation			
subjects affected / exposed	12 / 43 (27.91%)	1 / 10 (10.00%)	
occurrences (all)	12	1	
Diarrhoea			
subjects affected / exposed	10 / 43 (23.26%)	1 / 10 (10.00%)	
occurrences (all)	10	1	
Gastrointestinal pain			
subjects affected / exposed	11 / 43 (25.58%)	0 / 10 (0.00%)	
occurrences (all)	11	0	
Ascites			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Skin reaction			
subjects affected / exposed	13 / 43 (30.23%)	2 / 10 (20.00%)	
occurrences (all)	13	2	
Alopecia			
subjects affected / exposed	12 / 43 (27.91%)	2 / 10 (20.00%)	
occurrences (all)	12	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 43 (20.93%)	7 / 10 (70.00%)	
occurrences (all)	9	7	
Myalgia			
subjects affected / exposed	6 / 43 (13.95%)	2 / 10 (20.00%)	
occurrences (all)	6	2	
Back pain			

subjects affected / exposed	11 / 43 (25.58%)	1 / 10 (10.00%)	
occurrences (all)	11	1	
Infections and infestations			
Infection			
subjects affected / exposed	10 / 43 (23.26%)	1 / 10 (10.00%)	
occurrences (all)	10	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	6 / 43 (13.95%)	1 / 10 (10.00%)	
occurrences (all)	6	1	
Hypophosphataemia			
subjects affected / exposed	15 / 43 (34.88%)	1 / 10 (10.00%)	
occurrences (all)	15	1	
Hypermagnesaemia			
subjects affected / exposed	2 / 43 (4.65%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Hypomagnesaemia			
subjects affected / exposed	29 / 43 (67.44%)	4 / 10 (40.00%)	
occurrences (all)	29	4	
Hyperkalaemia			
subjects affected / exposed	22 / 43 (51.16%)	5 / 10 (50.00%)	
occurrences (all)	22	5	
Hypokalaemia			
subjects affected / exposed	4 / 43 (9.30%)	0 / 10 (0.00%)	
occurrences (all)	4	0	
Hypercalcaemia			
subjects affected / exposed	5 / 43 (11.63%)	2 / 10 (20.00%)	
occurrences (all)	5	2	
Hypocalcaemia			
subjects affected / exposed	24 / 43 (55.81%)	3 / 10 (30.00%)	
occurrences (all)	24	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 September 2018	Amendment 1 (Version 3.0 19-SEP-2018) of the study protocol included the following changes: • Exclusion criteria 2: Subjects who had previously received a CDK4/6 inhibitor was deleted • Due to safety reasons, tamoxifen was excluded from the list of ET which could be given to the patient at the discretion of the investigator. Tamoxifen could potentially increase the QT interval, a known toxicity also of ribociclib • Herbal medication was deleted from the list of prohibited medications • Surgery for primary tumor was permitted at the discretion of the investigator.
22 January 2020	Amendment 2 (Version 4.0 22-JAN-2020) included changes in study design and statistical assumptions, but it was not approved by the ethics committee.
18 June 2020	Amendment 3 (Version 5.0 18-JUN-2020) included the following changes: • Change of study design from two arms into one arm • Reduction of number of patients to be enrolled • Extension of the recruiting period.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
31 December 2021	Due to slow accrual of the trial, and in accordance with the IDMC recommendations, the trial was prematurely stopped.	-

Notes:

Limitations and caveats

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

Low number of patients recruited, the changes in study designs that have occurred throughout the trial, in addition to the premature termination of the study.

Notes: