NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

ribociclib (LEE011) in combination with letrozole

Trial Indication(s)

hormone-receptor positive, HER2-negative locally advanced or metastatic breast cancer.

Protocol Number

CLEE011XDE01

Protocol Title

A national phase IIIb, multi-center, open label study for women and men with hormone-receptor positive, HER-2 negative locally advanced or metastatic breast cancer treated with ribociclib (LEE011) in combination with letrozole

Clinical Trial Phase

Phase 3

Phase of Drug Development

Phase IIIb

Study Start/End Dates

Study Start Date: October 2016 (Actual)
Primary Completion Date: December 2018 (Actual)
Study Completion Date: February 2020 (Actual)

Reason for Termination (If applicable)

NA

Study Design/Methodology

This was a national, multi-center, open-label, phase IIIb trial to determine the efficacy and safety of treatment with ribociclib (LEE011) plus letrozole in patients with HR+, HER2-negative advanced (recurrent or metastatic) breast cancer. Patients were treated with daily doses of 600 mg ribociclib (3-weeks-on/1-week-off schedule) in combination with 2.5 mg letrozole daily (continuous dosing). Dose adjustments (dose reduction or interruption) according to safety findings were allowed.

Centers

Germany(87)

Objectives:

The primary objective of this study was the assessment of the clinical benefit rate (CBR) after 24 weeks for the total population and for cohorts A and B separately:

- To assess the CBR after 24 weeks for ribociclib (LEE011) in combination with letrozole among postmenopausal women and men with hormone receptor positive, HER2- negative, advanced breast cancer who received no prior treatment for advanced disease. (70% group) (Cohort A)
- To assess the CBR after 24 weeks for ribociclib (LEE011) in combination with letrozole and goserelin among pre-, and perimenopausal women who received no prior treatment for advanced disease as well as pre-, peri- and postmenopausal women and men with hormone receptor positive, HER2- negative, advanced breast cancer who received no more than 1 prior chemotherapy and 2 prior lines of endocrine therapy for advanced disease (30% group) (Cohort B)

Secondary objectives were:

- To assess the CBR after 24 weeks among pre- and perimenopausal women without prior therapy for advanced disease (Cohort B1)
- To assess the CBR after 24 weeks for ribociclib among pre-, peri- and postmenopausal women and men who were pretreated for advanced disease (Cohort B2)
- Progression-free survival (PFS) for the three different populations (postmenopausal women and men without prior treatment for advanced disease [Cohort A], pre- or perimenopausal women without prior treatment for advanced disease [Cohort B1], pre-, peri-, or postmenopausal women and men pretreated for advanced disease [Cohort B2])
- Overall survival (OS) for the three different populations, defined as the time from date of start of treatment to date of death due to any cause.
- Overall response rate (ORR) for the three different populations, defined as complete response (CR) or partial response (PR) as defined by RECIST 1.1
- To evaluate the safety and tolerability of ribociclib in combination with letrozole (and goserelin in premenopausal patients)
- To evaluate patient reported outcomes for health related quality of life (HRQOL)

Test Product (s), Dose(s), and Mode(s) of Administration

Ribociclib was administered as a tablet for oral use at a once daily dose of 600 mg (3 x 200 mg) for days 1-21 of each 28-day cycle.

Letrozole was administered as a tablet for oral use at a once daily dose.

Goserelin (for premenopausal patients) was administered as a subcutaneous implant at a dose of 3.6 mg on day 1 of each cycle.

Statistical Methods

In this single-arm trial, the primary objective was to estimate the CBR. Therefore, no statistical hypothesis or model underlined the analysis.

The CBR is the proportion of patients with a best overall response (BOR) of CR or PR or stable disease (SD) or neither complete response nor progressive disease (NCRNPD) within Week 24. The best overall response for each patient was determined from the sequence of investigator assessed overall lesion responses until week 24 according to RECIST 1.1. To be assigned a best overall response of CR, at least two determinations of CR at least 4 weeks apart before progression were required. To be assigned a best overall response of PR, at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) were required. To be assigned a SD, two determinations of SD at least 12 weeks apart (and not qualifying for PR or CR) were required.

Patients with a best overall response “unknown” were summarized by reason for having unknown status. Method changes were evaluated and assessed during the data review process.

The CBR (best overall response of CR or PR or SD or NCRNPD) as well as individual response categories (CR, PR, SD, PD, NCRNPD or unknown) were summarized using frequency tables together with their associated two-sided exact 95% confidence intervals (Clopper-Pearson method).

The Full Analysis Set (FAS) was used for the primary efficacy analysis, the PPS served for sensitivity analysis. Further, selected analysis tables were displayed as sensitivity analysis for a modified FAS population which included the patients from the study sites with a relevant inspection finding. The SAF was used for safety analysis and included all treated patients for full transparency. In a modified SAF population, patients with relevant inspection findings were excluded for consistency.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Patient is an adult, ≥ 18 years old at the time of informed consent and has signed informed consent before any trial related activities and according to local guidelines
- Women and men with advanced (locoregionally recurrent or metastatic) breast cancer not amenable to curative therapy.
- Patient has a histologically and/or cytologically confirmed diagnosis of estrogen-receptor positive and/or progesterone receptor positive and HER2-negative breast cancer by local laboratory. Local pathology is sufficient for assessment.
- Patient must have either:

a) Measurable disease, i.e., at least one measurable lesion as per RECIST 1.1 criteria).
b) Bone lesions: lytic or mixed (lytic + sclerotic) in the absence of measurable disease
c) Non-measurable disease

- Patient has an Eastern Cooperative Oncology Group (ECOG) performance status ≤2

Exclusion Criteria
- Patient who received any CDK4/6 inhibitor or any mTOR inhibitor.
- Patient has a known hypersensitivity to any of the excipients of ribociclib or letrozole
- Patients with current inflammatory breast cancer.
- Patient has received > 1 chemotherapy for the treatment of advanced/metastatic breast cancer
- Patient has received > 2 endocrine therapies for the treatment of advanced/metastatic breast cancer
- Patient has central nervous system (CNS) involvement.

If patient is fulfilling the following 3 criteria she/he is eligible for the trial.
a) completed prior therapy (including radiation and/or surgery) for CNS metastases ≥ 28 days prior to the start of study and
b) CNS tumor is clinically stable at the time of screening and
c) Patient is not receiving steroids and enzyme inducing anti-epileptic medications for brain metastases
- Patient has active cardiac disease or a history of cardiac dysfunction

Participant Flow Table

Overall Study

	ribociclib + letrozole cohort A	ribociclib + letrozole cohort B1	ribociclib + letrozole cohort B2	Total
Arm/Group Description	postmenopausal women, or men; naïve. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily.	premenopausal women or perimenopausal women; naïve All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received	premenopausal women or perimenopausal women or postmenopausal women, or men; pre-treated. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients	

		goserelin 3.6 mg i.m. monthly	additionally received goserelin 3.6 mg i.m. monthly	
Started	319	26	157	502
Full Analysis Set	307	26	154	487
Completed	100[1]	6[1]	19[1]	125
Not Completed	219	20	138	377
not specified	2	1	2	5
Lost to Follow-up	1	0	1	2
Death	6	0	2	8
Protocol Violation	3	0	6	9
Physician Decision	12	2	8	22
Withdrawal by Subject	24	1	12	37
Adverse Event	72	6	28	106
Progressive disease	97	10	78	185
Non-compliance with study medication	1	0	0	1
New therapy for study indication	1	0	1	2

[1] Only the primary reason for disc. is included in this table.

Baseline Characteristics

	ribociclib + letrozole cohort A	ribociclib + letrozole cohort B1	ribociclib + letrozole cohort B2	Total
Arm/Group Description	postmenopausal women, or men; naïve. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily.	premenopausal women or perimenopausal women; naïve All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly	premenopausal women or perimenopausal women or postmenopausal women, or men; pre-treated. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly	
Number of Participants [units: participants]	319	26	157	502
Age Categorical (units: Participants) Count of Participants (Not Applicable)				
<=18 years	0	0	0	0
Between 18 and 65 years	143	26	87	256
>=65 years	176	0	70	246

Age Continuous (units: Years) Mean ± Standard Deviation				
	65.7±10.1	46.5±4.9	62.8±12.8	63.8±11.6
Sex: Female, Male (units: Participants) Count of Participants (Not Applicable)				
Female	315	26	156	497
Male	4	0	1	5
Race (NIH/OMB) (units: Participants) Count of Participants (Not Applicable)				
American Indian or Alaska Native	0	0	0	0
Asian	0	1	1	2
Native Hawaiian or Other Pacific Islander	0	0	0	0
Black or African American	0	1	0	1
White	312	24	151	487
More than one race	1	0	3	4
Unknown or Not Reported	6	0	2	8

Primary Outcome Result(s)

Clinical Benefit Rate (CBR) in women and men with hormone receptor positiv, HER-2 negative breast cancer treated with ribocilib and letrozole

(Time Frame: At 24 weeks after last patient enrolled in trial)

	ribociclib + letrozole cohort A	ribociclib + letrozole cohort B1	ribociclib + letrozole cohort B2	Total
Arm/Group Description	postmenopausal women, or men; naïve. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily.	premenopausal women or perimenopausal women; naïve All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly	premenopausal women or perimenopausal women or postmenopausal women, or men; pre-treated. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly	Cohort A and Cohort B combined
Number of Participants Analyzed [units: participants]	307	26	154	487
Clinical Benefit Rate (CBR) in women and men with hormone receptor positiv, HER-2 negative breast cancer treated with ribocilib and letrozole (units: Percentage of Participants) Number (95% Confidence Interval)				
CBR by week 24 (= BOR of CR or PR or SD or NCRNPD(Confirmed Best Overall Response (BOR))	63.2 (57.5 to 68.6)	57.7 (36.9 to 76.6)	56.5 (48.3 to 64.5)	60.8 (56.3 to 65.1)

CBR by week 24 (= BOR of CR or PR or SD or NCRNPD (non-confirmed BOR)	71.7 (66.3 to 76.6)	69.2 (48.2 to 85.7)	64.3 (56.2 to 71.8)	69.2 (64.9 to 73.3)

Secondary Outcome Result(s)

Progression free survival (PFS) for different populations - Kaplan-Meier estimates (%, 95% CI)

(Time Frame: At week 24 , week 48 and week 72)

	ribociclib + letrozole cohort A	ribociclib + letrozole cohort B1	ribociclib + letrozole cohort B2
Arm/Group Description	postmenopausal women, or men; naïve. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily.	premenopausal women or perimenopausal women; naïve All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly	premenopausal women or perimenopausal women or postmenopausal women, or men; pre-treated. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly
Number of Participants Analyzed [units: participants]	307	26	154

Progression free survival (PFS) for different populations - Kaplan-Meier estimates (%, 95% CI)
(units: Percentage of Participants)
Number (95% Confidence Interval)

Kaplan-Meier estimates (%, 95% CI) - Week 24	73.1 (67.3 to 77.9)	67.0 (44.7 to 82.0)	63.8 (55.2 to 71.3)
Kaplan-Meier estimates (%, 95% CI) - Week 48	61.9 (55.7 to 67.5)	58.7 (36.8 to 75.2)	47.5 (38.7 to 55.7)
Kaplan-Meier estimates (%, 95% CI) - week 72	54.5 (48.1 to 60.5)	49.6 (28.6 to 67.6)	39.3 (30.8 to 47.6)

Progression free survival (PFS) for different populations - Median time to progression or death with 95% CI [months]

(Time Frame: Up to approximately month 25)

	ribociclib + letrozole cohort A	ribociclib + letrozole cohort B1	ribociclib + letrozole cohort B2
Arm/Group Description	postmenopausal women, or men; naïve. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily.	premenopausal women or perimenopausal women; naïve All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly	premenopausal women or perimenopausal women or postmenopausal women, or men; pre-treated. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly

Number of Participants Analyzed [units: participants]	307	26	154
Progression free survival (PFS) for different populations - Median time to progression or death with 95% CI [months] (units: Months) Median (95% Confidence Interval)			
Median time to progression or death with 95% CI	21.8 (13.9 to 25.3)	16.5 (3.2 to NA)[1]	8.8 (8.1 to 16.3)

[1] The upper limit was not estimable. Existence of the confidence limits does not directly depend on the Kaplan-Meier curve itself (dropping below 0.75, 0.5 or 0.25), but on the curves that represent the confidence limits (CL) for the survivor function. They envelop the Kaplan-Meier curve.

Overall Survival (OS) - Kaplan-Meier estimates (%, 95% CI)

(Time Frame: At Week 24, Week 48 and Week 72)

	ribociclib + letrozole cohort A	**ribociclib + letrozole cohort B1**	**ribociclib + letrozole cohort B2**
Arm/Group Description	postmenopausal women, or men; naïve. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily.	premenopausal women or perimenopausal women; naïve All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received	premenopausal women or perimenopausal women or postmenopausal women, or men; pre-treated. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients

		goserelin 3.6 mg i.m. monthly	additionally received goserelin 3.6 mg i.m. monthly
Number of Participants Analyzed [units: participants]	307	26	154
Overall Survival (OS) - Kaplan-Meier estimates (%, 95% CI) (units: Percentage of Participants) Number (95% Confidence Interval)			
Kaplan-Meier estimates (%, 95% CI) - Week 24	98.6 (96.4 to 99.5)	100.0 (100.0 to 100.0)	93.9 (88.5 to 96.8)
Kaplan-Meier estimates (%, 95% CI) - Week 48	93.3 (89.7 to 95.7)	87.5 (66.1 to 95.8)	86.1 (79.2 to 90.8)
Kaplan-Meier estimates (%, 95% CI) - Week 72	89.7 (85.5 to 92.7)	87.5 (66.1 to 95.8)	81.0 (73.5 to 86.6)

Overall Survival (OS) - Median time to progression or death with 95% CI [months]

(Time Frame: Up to approximatley 38 months)

	ribociclib + letrozole cohort A	**ribociclib + letrozole cohort B1**	**ribociclib + letrozole cohort B2**
Arm/Group Description	postmenopausal women, or men; naïve. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily.	premenopausal women or perimenopausal women; naïve All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally	premenopausal women or perimenopausal women or postmenopausal women, or men; pre-treated. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal

		received goserelin 3.6 mg i.m. monthly	patients additionally received goserelin 3.6 mg i.m. monthly
Number of Participants Analyzed [units: participants]	307	26	154
Overall Survival (OS) - Median time to progression or death with 95% CI [months] (units: Months) Median (95% Confidence Interval)			
Median time to death due to any cause, with 95% CI [months]	NA (NA to NA)[123]	NA (30.9 to NA)[123]	NA (31.0 to NA)[123]

[1] Not estimable. Existence of the confidence limits does not directly depend on the Kaplan-Meier curve itself (dropping below 0.75, 0.5 or 0.25), but on the curves that represent the confidence limits (CL) for the survivor function. They envelop the Kaplan-Meier curve.
[2] Not estimable. Existence of the confidence limits does not directly depend on the Kaplan-Meier curve itself (dropping below 0.75, 0.5 or 0.25), but on the curves that represent the confidence limits (CL) for the survivor function. They envelop the Kaplan-Meier curve.
[3] Not estimable. Existence of the confidence limits does not directly depend on the Kaplan-Meier curve itself (dropping below 0.75, 0.5 or 0.25), but on the curves that represent the confidence limits (CL) for the survivor function. They envelop the Kaplan-Meier curve.

Overall Survival (OS) - number of censored participants and number of deaths

(Time Frame: Up to approximatley 38 months)

	ribociclib + letrozole cohort A	**ribociclib + letrozole cohort B1**	**ribociclib + letrozole cohort B2**
Arm/Group Description	postmenopausal women, or men; naïve. All patients received ribociclib 600mg p.o. daily +	premenopausal women or perimenopausal women; naïve All patients received ribociclib 600mg p.o.	premenopausal women or perimenopausal women or postmenopausal women, or men; pre-treated. All patients

	Letrozole 2.5 mg p.o. daily.	daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly	received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly
Number of Participants Analyzed [units: participants]	307	26	154
Overall Survival (OS) - number of censored participants and number of deaths (units: Participants)			
No. of censored (no death), n	240	17	94
No. of events (deaths due to any cause), n	67	9	60

Overall response rate (ORR) - Kaplan-Meier estimates (%, 95% CI)

(Time Frame: At week 24)

	ribociclib + letrozole cohort A	**ribociclib + letrozole cohort B1**	**ribociclib + letrozole cohort B2**
Arm/Group Description	postmenopausal women, or men; naïve. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily.	premenopausal women or perimenopausal women; naïve All patients received ribociclib 600mg p.o. daily +	premenopausal women or perimenopausal women or postmenopausal women, or men; pre-treated. All patients received

		Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly	ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly
Number of Participants Analyzed [units: participants]	307	26	154
Overall response rate (ORR) - Kaplan-Meier estimates (%, 95% CI) (units: Percentage of Participants) Number (95% Confidence Interval)			
ORR by week 24 - (BOR of CR or PR) (confirmed)	22.8 (18.2 to 27.9)	23.1 (9.0 to 43.6)	11.7 (7.1 to 17.8)
ORR by week 24 - (BOR of CR or PR) (unconfirmed)	24.8 (20.0 to 30.0)	30.8 (14.3 to 51.8)	16.2 (10.8 to 23.0)

Change from baseline at week 24 of patient reported Quality of Life (QoL) via EORTC QLQ-C30

(Time Frame: Change from Baseline to Week 24)

	ribociclib + letrozole cohort A	**ribociclib + letrozole cohort B1**	**ribociclib + letrozole cohort B2**	**ribociclib + letrozole cohort B**
Arm/Group Description	postmenopausal women, or men; naïve. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily.	premenopausal women or perimenopausal women; naïve All patients received ribociclib 600mg p.o. daily + Letrozole 2.5	premenopausal women or perimenopausal women or postmenopausal women, or men; pre-treated. All patients received ribociclib 600mg	premenopausal women or perimenopausal women or postmenopausal women, or men; naïve + pre-treated All patients received

		mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly	p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly	ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o.daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly
Number of Participants Analyzed [units: participants]	307	26	154	180
Change from baseline at week 24 of patient reported Quality of Life (QoL) via EORTC QLQ-C30 (units: Scores on a scale) Mean ± Standard Deviation				
Global health status - Change from baseline at Week 24 (C7D1) (n=181,15,75,90)	8.8 ± 23.7	11.7 ± 20.8	5.0 ± 26.2	6.1 ± 25.4
Physical Functioning - Change from baseline at Week 24 (C7D1) (n=183,15,75,90)	-3.1 ± 19.9	-3.6 ± 10.7	-2.2 ± 17.7	-2.4 ± 16.7
Role Functioning - Change from baseline at Week 24 (C7D1) (n=182,15,75,90)	-6.6 ± 31.9	-17 ± 21.8	-1.3 ± 34.7	-3.9 ± 33.3
Emotional Functioning - Change from baseline at Week 24 (C7D1) (n=182,15,75,90)	-9.6 ± 24.2	-9.4 ± 25.0	-3.6 ± 21.8	-4.6 ± 22.4
Cognitive Functioning - Change from baseline at Week 24 (C7D1) (n=182,15,75,90)	2.7 ± 23.7	2.2 ± 28.1	1.1 ± 21.6	1.3 ± 22.7
Social Functioning - Change from baseline at	-6.9 ± 27.9	-16 ± 21.3	-5.3 ± 31.3	-7.0 ± 30.0

Week 24 (C7D1) (n=181,15,75,90)				
Fatigue - Change from baseline at Week 24 (C7D1) (n=182,15,75,90)	6.3 ± 25.9	11.1 ± 20.6	3.9 ± 27.1	5.1 ± 26.1
Nausea / Vomiting - Change from baseline at Week 24 (C7D1) (n=182,15,75,90)	0.1 ± 16.7	1.1 ± 22.2	-4.9 ± 19.1	-3.9 ± 19.7
Pain - Change from baseline at Week 24 (C7D1) (n=182,15,74,89)	13.2 ± 31.9	15.6 ± 24.8	9.0 ± 27.6	10.1 ± 27.1
Dyspnoea - Change from baseline at Week 24 (C7D1) (n=182,15,75,90)	3.8 ± 32.4	4.4 ± 21.3	-5.3 ± 30.5	-3.7 ± 29.3
Insomnia - Change from baseline at Week 24 (C7D1) (n=183, 15,75,90)	4.2 ± 33.2	6.7 ± 31.4	4.9 ± 32.7	5.2 ± 32.3
Appetite loss - Change from baseline at Week 24 (C7D1) (n=181, 15, 74, 89)	11.2 ± 33.7	6.7 ± 28.7	1.4 ± 30.9	2.2 ± 30.5
Constipation - Change from baseline at Week 24 (C7D1) (n=183,15,74,89)	-2.7 ± 26.6	2.2 ± 26.6	-3.6 ± 27.9	-2.6 ± 27.6
Diarrhea - Change from baseline at Week 24 (C7D1) (n=182,15,74,89)	2.6 ± 24.6	0.0 ± 45.4	2.3 ± 27.2	1.9 ± 30.7
Financial Problems - Change from baseline at Week 24 (C7D1) (n=179,15,73,88)	0.2 ± 27.7	-4.4 ± 24.8	-1.4 ± 25.1	-1.9 ± 24.9

Patient reported Quality of Life (QoL) via EORTC BR-23 - change from baseline at Week 24 (Cycle 7)

(Time Frame: Baseline and Week 24 (Cycle 7))

	ribociclib + letrozole cohort A	ribociclib + letrozole cohort B1	ribociclib + letrozole cohort B2	ribociclib + letrozole cohort B
Arm/Group Description	postmenopausal women, or men; naïve. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily.	premenopausal women or perimenopausal women; naïve All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly	premenopausal women or perimenopausal women or postmenopausal women, or men; pre-treated. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly	premenopausal women or perimenopausal women or postmenopausal women, or men; naïve + pre-treated All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o.daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly
Number of Participants Analyzed [units: participants]	307	26	154	180
Patient reported Quality of Life (QoL) via EORTC BR-23 - change from baseline at Week 24 (Cycle 7) (units: Scores on a scale) Mean ± Standard Deviation				
EORTC QLQ-BR23 BODY IMAGE during the study - change from baseline at cycle 7 (n=167,15,72,87)	-1.5 ± 18.2	-0.6 ± 22.2	0.4 ± 22.7	0.2 ± 22.5
EORTC QLQ-BR23 SEXUAL FUNCTIONING - change from baseline at cycle 7 (n=120,13,60,73)	-1.1 ± 17.7	0.0 ± 24.5	0.8 ± 18.0	0.7 ± 19.1

EORTC QLQ-BR23 SEXUAL ENJOYMENT during the study - change from baseline at cycle 7 (n=18,2,18,20)	-1.9 ± 31.3	-17 ± 23.6	7.4 ± 26.9	5.0 ± 27.1
EORTC QLQ-BR23 FUTURE PERSPECTIVE - change from baseline at cycle 7 (n=172,15,74,89)	-20 ± 33.4	-24 ± 26.6	-12 ± 26.2	-14 ± 26.5
EORTC QLQ-BR23 SYSTEMATIC THERAPY - change from baseline at cycle 7 (n=180,15,74,89)	-9.4 ± 16.6	-13 ± 22.3	-6.0 ± 14.9	-7.1 ± 16.4
EORTC QLQ-BR23 BREAST SYMPTOMS during the study - change from baseline at cycle 7 (n=172,15,73,88)	3.3 ± 15.7	8.3 ± 22.7	0.9 ± 17.5	2.2 ± 18.6
EORTC QLQ-BR23 ARM SYMPTOMS during the study - change from baseline at cycle 7 (n=175,15,74,89)	4.1 ± 21.1	-1.5 ± 22.6	-2.1 ± 18.1	-2.0 ± 18.8
EORTC QLQ-BR23 HAIR LOSS during the study - change from baseline at cycle 7 (n=23, 2,14,16)	-22 ± 43.4	-17 ± 23.6	-14 ± 33.9	-15 ± 32.1

Time to 10% deterioration in EORTC global health status

(Time Frame: up to approximately 10 months)

	ribociclib + letrozole cohort A	ribociclib + letrozole cohort B1	ribociclib + letrozole cohort B2	Total

Arm/Group Description	postmenopausal women, or men; naïve. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily.	premenopausal women or perimenopausal women; naïve All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly	premenopausal women or perimenopausal women or postmenopausal women, or men; pre-treated. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly	Cohorts A, B1 and B2 combined
Number of Participants Analyzed [units: participants]	307	26	154	487
Time to 10% deterioration in EORTC global health status (units: months) Median (95% Confidence Interval)				
	3.3 (2.8 to 4.6)	3.7 (1.8 to 10.1)	2.8 (1.8 to 4.6)	3.0 (2.8 to 4.6)

Number of Participants with Treatment Emergent Adverse Events (TEAE)

(Time Frame: Up to Week 72)

	ribociclib + letrozole cohort A	ribociclib + letrozole cohort B1	ribociclib + letrozole cohort B2

Arm/Group Description	postmenopausal women, or men; naïve. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily.	premenopausal women or perimenopausal women; naïve All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly	premenopausal women or perimenopausal women or postmenopausal women, or men; pre-treated. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly
Number of Participants Analyzed [units: participants]	319	26	157
Number of Participants with Treatment Emergent Adverse Events (TEAE) (units: Number of Participants)			
Total AEs (i.e., Includes any type of AE.)	318	25	157
Serious AEs	97	5	45
Non-serious AEs	317	25	157
AEs with suspected relationship to ribociclib	302	25	144
AEs leading to discontinuation of ribociclib	76	7	38
AEs with fatal outcome	6	0	6

Post-Hoc All Collected Deaths

(Time Frame: on-treatment deaths: up to approx 3.15 years; all deaths: approx 3.15 years)

	ribociclib + letrozole cohort A	ribociclib + letrozole cohort B1	ribociclib + letrozole cohort B2	Total
Arm/Group Description	postmenopausal women, or men; naïve. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily.	premenopausal women or perimenopausal women; naïve All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly	premenopausal women or perimenopausal women or postmenopausal women, or men; pre-treated. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally rec	Cohort A and Cohort B combined
Number of Participants Analyzed [units: participants]	319	26	157	502
All Collected Deaths (units: Participants)				
on-treatment deaths	6	0	6	12
Total deaths (n=307,26,154,487)	67	9	60	136

Safety Results

All-Cause Mortality

	ribociclib + letrozole cohort A N = 319	ribociclib + letrozole cohort B N = 183	ribociclib + letrozole cohort B1 N = 26	ribociclib + letrozole cohort B2 N = 157	Total N = 502
Arm/Group Description	postmenopausal women, or men; naïve. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily.	premenopausal women or perimenopausal women or postmenopausal women, or men; naïve + pre-treated All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o.daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly	premenopausal women or perimenopausal women; naïve All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly	premenopausal women or perimenopausal women or postmenopausal women, or men; pre-treated. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly	Total
Total participants affected	6 (1.88%)	6 (3.28%)	0 (0.00%)	6 (3.82%)	12 (2.39%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse events were reported from first dose of study treatment until end of study treatment plus 30 days, up to a maximum duration of 1150 days (approx. 3.15 years).(Treatment duration ranged from 2 days to 1120 days.)
Additional Description	For this study, disease progression was NOT classified as an Adverse Event.
Source Vocabulary for Table Default	MedDRA (22.1)
Assessment Type for Table Default	Systematic Assessment

	ribociclib + letrozole cohort A N = 319	**ribociclib + letrozole cohort B N = 183**	**ribociclib + letrozole cohort B1 N = 26**	**ribociclib + letrozole cohort B2 N = 157**	**Total N = 502**
Arm/Group Description	postmenopausal women, or men; naïve. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily.	premenopausal women or perimenopausal women or postmenopausal women, or men; naïve + pre-treated All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o.daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly	premenopausal women or perimenopausal women; naïve All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly	premenopausal women or perimenopausal women or postmenopausal women, or men; pre-treated. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly	Total
Total participants affected	97 (30.41%)	50 (27.32%)	5 (19.23%)	45 (28.66%)	147 (29.28%)

BLOOD AND LYMPHATIC SYSTEM DISORDERS					
ANAEMIA	4 (1.25%)	4 (2.19%)	0 (0.00%)	4 (2.55%)	8 (1.59%)
DISSEMINATED INTRAVASCULAR COAGULATION	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
FEBRILE NEUTROPENIA	0 (0.00%)	3 (1.64%)	1 (3.85%)	2 (1.27%)	3 (0.60%)
HYPERFIBRINOLYSIS	0 (0.00%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	1 (0.20%)
LEUKOPENIA	2 (0.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.40%)
NEUTROPENIA	2 (0.63%)	2 (1.09%)	0 (0.00%)	2 (1.27%)	4 (0.80%)
PANCYTOPENIA	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
THROMBOCYTOPENIA	3 (0.94%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (0.60%)
CARDIAC DISORDERS					
ATRIAL FIBRILLATION	2 (0.63%)	2 (1.09%)	0 (0.00%)	2 (1.27%)	4 (0.80%)
BRADYARRHYTHMIA	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
CARDIAC ARREST	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
CARDIAC FAILURE	1 (0.31%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	2 (0.40%)
MYOCARDIAL INFARCTION	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
SUPRAVENTRICULAR TACHYCARDIA	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
ENDOCRINE DISORDERS					
HYPERTHYROIDISM	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
GASTROINTESTINAL DISORDERS					
ABDOMINAL PAIN	1 (0.31%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	2 (0.40%)

ABDOMINAL PAIN LOWER	0 (0.00%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	1 (0.20%)
ANAL HAEMORRHAGE	0 (0.00%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	1 (0.20%)
CONSTIPATION	2 (0.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.40%)
DIARRHOEA	3 (0.94%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	4 (0.80%)
GASTRITIS	3 (0.94%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (0.60%)
GASTROOESOPHAGEAL REFLUX DISEASE	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
ILEUS	1 (0.31%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	2 (0.40%)
INTESTINAL STRANGULATION	0 (0.00%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	1 (0.20%)
NAUSEA	7 (2.19%)	2 (1.09%)	0 (0.00%)	2 (1.27%)	9 (1.79%)
VOMITING	3 (0.94%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (0.60%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS					
CHEST PAIN	1 (0.31%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	2 (0.40%)
COMPLICATION OF DEVICE INSERTION	0 (0.00%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	1 (0.20%)
DEATH	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
FATIGUE	0 (0.00%)	2 (1.09%)	0 (0.00%)	2 (1.27%)	2 (0.40%)
GENERAL PHYSICAL HEALTH DETERIORATION	2 (0.63%)	5 (2.73%)	0 (0.00%)	5 (3.18%)	7 (1.39%)
IMPAIRED HEALING	1 (0.31%)	2 (1.09%)	0 (0.00%)	2 (1.27%)	3 (0.60%)
OEDEMA PERIPHERAL	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
PAIN	1 (0.31%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	2 (0.40%)
PYREXIA	6 (1.88%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	7 (1.39%)

HEPATOBILIARY DISORDERS					
BILE DUCT STENOSIS	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
BILIARY COLIC	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
CHOLECYSTITIS	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
CHOLECYSTITIS ACUTE	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
CHOLELITHIASIS	2 (0.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.40%)
DRUG-INDUCED LIVER INJURY	5 (1.57%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	6 (1.20%)
HEPATIC CIRRHOSIS	0 (0.00%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	1 (0.20%)
HEPATOTOXICITY	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
JAUNDICE	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
INFECTIONS AND INFESTATIONS					
ABDOMINAL ABSCESS	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
ABSCESS JAW	0 (0.00%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	1 (0.20%)
APPENDICITIS	0 (0.00%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	1 (0.20%)
ATYPICAL PNEUMONIA	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
BRONCHITIS	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
CHOLECYSTITIS INFECTIVE	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
CYSTITIS	0 (0.00%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	1 (0.20%)
CYSTITIS ESCHERICHIA	0 (0.00%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	1 (0.20%)
DEVICE RELATED INFECTION	0 (0.00%)	2 (1.09%)	0 (0.00%)	2 (1.27%)	2 (0.40%)
DIVERTICULITIS	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
EMPHYSEMATOUS CHOLECYSTITIS	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)

ERYSIPELAS	3 (0.94%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (0.60%)
ESCHERICHIA INFECTION	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
FEBRILE INFECTION	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
GASTROENTERITIS	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
GASTROINTESTINAL INFECTION	1 (0.31%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	2 (0.40%)
HELICOBACTER GASTRITIS	0 (0.00%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	1 (0.20%)
INFECTIOUS PLEURAL EFFUSION	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
INFLUENZA	0 (0.00%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	1 (0.20%)
MASTITIS	0 (0.00%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	1 (0.20%)
PNEUMONIA	8 (2.51%)	2 (1.09%)	0 (0.00%)	2 (1.27%)	10 (1.99%)
PROTEUS INFECTION	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
PYELONEPHRITIS	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
RESPIRATORY SYNCYTIAL VIRUS INFECTION	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
SEPSIS	1 (0.31%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	2 (0.40%)
UPPER RESPIRATORY TRACT INFECTION	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
URINARY TRACT INFECTION	3 (0.94%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (0.60%)
UROSEPSIS	2 (0.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.40%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS					
ACCIDENT	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)

ANKLE FRACTURE	0 (0.00%)	1 (0.55%)	1 (3.85%)	0 (0.00%)	1 (0.20%)
CERVICAL VERTEBRAL FRACTURE	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
FALL	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
FEMORAL NECK FRACTURE	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
FEMUR FRACTURE	3 (0.94%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (0.60%)
HIP FRACTURE	0 (0.00%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	1 (0.20%)
HUMERUS FRACTURE	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
INCISIONAL HERNIA	0 (0.00%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	1 (0.20%)
JAW FRACTURE	0 (0.00%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	1 (0.20%)
POST PROCEDURAL HAEMORRHAGE	0 (0.00%)	1 (0.55%)	1 (3.85%)	0 (0.00%)	1 (0.20%)
POSTOPERATIVE ADHESION	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
POST-TRAUMATIC PAIN	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
PROCEDURAL COMPLICATION	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
RADIUS FRACTURE	0 (0.00%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	1 (0.20%)
RIB FRACTURE	3 (0.94%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (0.60%)
TIBIA FRACTURE	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
UPPER LIMB FRACTURE	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
INVESTIGATIONS					
ALANINE AMINOTRANSFERASE INCREASED	5 (1.57%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	6 (1.20%)

ASPARTATE AMINOTRANSFERASE INCREASED	3 (0.94%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	4 (0.80%)
BLOOD BILIRUBIN INCREASED	1 (0.31%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	2 (0.40%)
C-REACTIVE PROTEIN INCREASED	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
HAEMOGLOBIN DECREASED	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
NEUTROPHIL COUNT DECREASED	0 (0.00%)	1 (0.55%)	1 (3.85%)	0 (0.00%)	1 (0.20%)
WHITE BLOOD CELL COUNT DECREASED	0 (0.00%)	1 (0.55%)	1 (3.85%)	0 (0.00%)	1 (0.20%)
METABOLISM AND NUTRITION DISORDERS					
DECREASED APPETITE	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
DEHYDRATION	1 (0.31%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	2 (0.40%)
HYPERCALCAEMIA	0 (0.00%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	1 (0.20%)
HYPERKALAEMIA	0 (0.00%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	1 (0.20%)
HYPONATRAEMIA	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
HYPOPHAGIA	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
TUMOUR LYSIS SYNDROME	0 (0.00%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	1 (0.20%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS					
ARTHRALGIA	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
BACK PAIN	2 (0.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.40%)
BONE LESION	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
BONE PAIN	2 (0.63%)	2 (1.09%)	0 (0.00%)	2 (1.27%)	4 (0.80%)

FLANK PAIN	0 (0.00%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	1 (0.20%)
LUMBAR SPINAL STENOSIS	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
MOBILITY DECREASED	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
MUSCULOSKELETAL CHEST PAIN	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
MUSCULOSKELETAL PAIN	1 (0.31%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	2 (0.40%)
OSTEITIS	0 (0.00%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	1 (0.20%)
OSTEOARTHRITIS	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
OSTEONECROSIS OF JAW	2 (0.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.40%)
PAIN IN EXTREMITY	2 (0.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.40%)
SPINAL PAIN	0 (0.00%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	1 (0.20%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)					
BRONCHIAL CARCINOMA	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
CANCER PAIN	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
COLON CANCER	0 (0.00%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	1 (0.20%)
MALIGNANT PLEURAL EFFUSION	2 (0.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.40%)
METASTASES TO BONE	0 (0.00%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	1 (0.20%)
METASTASES TO SPINE	0 (0.00%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	1 (0.20%)
RENAL CELL CARCINOMA	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)

SQUAMOUS CELL CARCINOMA OF THE TONGUE	0 (0.00%)	1 (0.55%)	1 (3.85%)	0 (0.00%)	1 (0.20%)
TUMOUR PAIN	0 (0.00%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	1 (0.20%)
NERVOUS SYSTEM DISORDERS					
CEREBRAL ISCHAEMIA	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
CEREBROVASCULAR ACCIDENT	2 (0.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.40%)
DIZZINESS	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
HEADACHE	0 (0.00%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	1 (0.20%)
MONOPLEGIA	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
NEUROPATHY PERIPHERAL	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
PARAESTHESIA	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
PERIPHERAL NERVE LESION	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
SYNCOPE	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
PRODUCT ISSUES					
DEVICE LOOSENING	0 (0.00%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	1 (0.20%)
PSYCHIATRIC DISORDERS					
DEPRESSION	0 (0.00%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	1 (0.20%)
PANIC ATTACK	0 (0.00%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	1 (0.20%)
SOMATIC SYMPTOM DISORDER	2 (0.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.40%)
RENAL AND URINARY DISORDERS					

ACUTE KIDNEY INJURY	5 (1.57%)	1 (0.55%)	1 (3.85%)	0 (0.00%)	6 (1.20%)
HAEMATURIA	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
KIDNEY CONGESTION	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
RENAL DISORDER	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
RENAL FAILURE	1 (0.31%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	2 (0.40%)
RENAL IMPAIRMENT	1 (0.31%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	2 (0.40%)
URETERIC STENOSIS	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
URETEROLITHIASIS	0 (0.00%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	1 (0.20%)
URINARY INCONTINENCE	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
URINARY RETENTION	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
URINARY TRACT OBSTRUCTION	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS					
PELVIC PAIN	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS					
ASTHMA	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
DYSPNOEA	9 (2.82%)	3 (1.64%)	0 (0.00%)	3 (1.91%)	12 (2.39%)
DYSPNOEA EXERTIONAL	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
HYPERVENTILATION	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
PLEURAL EFFUSION	3 (0.94%)	3 (1.64%)	0 (0.00%)	3 (1.91%)	6 (1.20%)
PNEUMONITIS	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
PNEUMOTHORAX	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)

PULMONARY EMBOLISM	7 (2.19%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	8 (1.59%)
PULMONARY FIBROSIS	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
RESPIRATORY FAILURE	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS					
SKIN ULCER	0 (0.00%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	1 (0.20%)
VASCULAR DISORDERS					
CIRCULATORY COLLAPSE	0 (0.00%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	1 (0.20%)
HYPERTENSION	0 (0.00%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	1 (0.20%)
HYPERTENSIVE CRISIS	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
HYPOTENSION	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)

Other Adverse Events by System Organ Class

Time Frame	Adverse events were reported from first dose of study treatment until end of study treatment plus 30 days, up to a maximum duration of 1150 days (approx. 3.15 years).(Treatment duration ranged from 2 days to 1120 days.)
Additional Description	For this study, disease progression was NOT classified as an Adverse Event.
Source Vocabulary for Table Default	MedDRA (22.1)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	ribociclib + letrozole	**ribociclib + letrozole**	**ribociclib + letrozole**	**ribociclib + letrozole**	**Total N = 502**

	cohort A N = 319	cohort B N = 183	cohort B1 N = 26	cohort B2 N = 157	
Arm/Group Description	postmenopausal women, or men; naïve. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily.	premenopausal women or perimenopausal women or postmenopausal women, or men; naïve + pre-treated All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o.daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly	premenopausal women or perimenopausal women; naïve All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly	premenopausal women or perimenopausal women or postmenopausal women, or men; pre-treated. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly	Total
Total participants affected	315 (98.75%)	181 (98.91%)	25 (96.15%)	156 (99.36%)	496 (98.80%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS					
ANAEMIA	46 (14.42%)	36 (19.67%)	7 (26.92%)	29 (18.47%)	82 (16.33%)
LEUKOPENIA	76 (23.82%)	39 (21.31%)	8 (30.77%)	31 (19.75%)	115 (22.91%)
LYMPHOPENIA	7 (2.19%)	2 (1.09%)	2 (7.69%)	0 (0.00%)	9 (1.79%)
NEUTROPENIA	162 (50.78%)	88 (48.09%)	15 (57.69%)	73 (46.50%)	250 (49.80%)
THROMBOCYTOPENIA	26 (8.15%)	18 (9.84%)	1 (3.85%)	17 (10.83%)	44 (8.76%)
EAR AND LABYRINTH DISORDERS					
VERTIGO	33 (10.34%)	17 (9.29%)	4 (15.38%)	13 (8.28%)	50 (9.96%)
EYE DISORDERS					

DRY EYE	23 (7.21%)	10 (5.46%)	2 (7.69%)	8 (5.10%)	33 (6.57%)
LACRIMATION INCREASED	34 (10.66%)	11 (6.01%)	2 (7.69%)	9 (5.73%)	45 (8.96%)
GASTROINTESTINAL DISORDERS					
ABDOMINAL PAIN	15 (4.70%)	14 (7.65%)	5 (19.23%)	9 (5.73%)	29 (5.78%)
ABDOMINAL PAIN UPPER	33 (10.34%)	13 (7.10%)	3 (11.54%)	10 (6.37%)	46 (9.16%)
CONSTIPATION	62 (19.44%)	32 (17.49%)	4 (15.38%)	28 (17.83%)	94 (18.73%)
DIARRHOEA	85 (26.65%)	40 (21.86%)	8 (30.77%)	32 (20.38%)	125 (24.90%)
DRY MOUTH	28 (8.78%)	10 (5.46%)	1 (3.85%)	9 (5.73%)	38 (7.57%)
DYSPEPSIA	25 (7.84%)	14 (7.65%)	2 (7.69%)	12 (7.64%)	39 (7.77%)
NAUSEA	130 (40.75%)	77 (42.08%)	9 (34.62%)	68 (43.31%)	207 (41.24%)
STOMATITIS	33 (10.34%)	27 (14.75%)	4 (15.38%)	23 (14.65%)	60 (11.95%)
TOOTHACHE	9 (2.82%)	4 (2.19%)	2 (7.69%)	2 (1.27%)	13 (2.59%)
VOMITING	66 (20.69%)	31 (16.94%)	5 (19.23%)	26 (16.56%)	97 (19.32%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS					
FATIGUE	123 (38.56%)	74 (40.44%)	15 (57.69%)	59 (37.58%)	197 (39.24%)
OEDEMA PERIPHERAL	35 (10.97%)	22 (12.02%)	5 (19.23%)	17 (10.83%)	57 (11.35%)
PYREXIA	23 (7.21%)	14 (7.65%)	4 (15.38%)	10 (6.37%)	37 (7.37%)
IMMUNE SYSTEM DISORDERS					
SEASONAL ALLERGY	4 (1.25%)	6 (3.28%)	3 (11.54%)	3 (1.91%)	10 (1.99%)
INFECTIONS AND INFESTATIONS					
BRONCHITIS	19 (5.96%)	5 (2.73%)	1 (3.85%)	4 (2.55%)	24 (4.78%)
CYSTITIS	21 (6.58%)	9 (4.92%)	3 (11.54%)	6 (3.82%)	30 (5.98%)

GASTROINTESTINAL INFECTION	2 (0.63%)	3 (1.64%)	2 (7.69%)	1 (0.64%)	5 (1.00%)
NASOPHARYNGITIS	94 (29.47%)	49 (26.78%)	10 (38.46%)	39 (24.84%)	143 (28.49%)
URINARY TRACT INFECTION	31 (9.72%)	17 (9.29%)	1 (3.85%)	16 (10.19%)	48 (9.56%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS					
ARTHROPOD BITE	3 (0.94%)	3 (1.64%)	2 (7.69%)	1 (0.64%)	6 (1.20%)
ARTHROPOD STING	0 (0.00%)	2 (1.09%)	2 (7.69%)	0 (0.00%)	2 (0.40%)
INVESTIGATIONS					
ALANINE AMINOTRANSFERASE INCREASED	75 (23.51%)	36 (19.67%)	6 (23.08%)	30 (19.11%)	111 (22.11%)
ASPARTATE AMINOTRANSFERASE INCREASED	66 (20.69%)	36 (19.67%)	5 (19.23%)	31 (19.75%)	102 (20.32%)
BLOOD BILIRUBIN INCREASED	16 (5.02%)	1 (0.55%)	0 (0.00%)	1 (0.64%)	17 (3.39%)
BLOOD CREATININE INCREASED	27 (8.46%)	12 (6.56%)	2 (7.69%)	10 (6.37%)	39 (7.77%)
BLOOD LACTATE DEHYDROGENASE INCREASED	17 (5.33%)	3 (1.64%)	1 (3.85%)	2 (1.27%)	20 (3.98%)
BLOOD THYROID STIMULATING HORMONE INCREASED	0 (0.00%)	2 (1.09%)	2 (7.69%)	0 (0.00%)	2 (0.40%)
ELECTROCARDIOGRAM QT PROLONGED	23 (7.21%)	14 (7.65%)	1 (3.85%)	13 (8.28%)	37 (7.37%)
GAMMA-GLUTAMYLTRANSFERASE INCREASED	33 (10.34%)	18 (9.84%)	5 (19.23%)	13 (8.28%)	51 (10.16%)

NEUTROPHIL COUNT DECREASED	40 (12.54%)	25 (13.66%)	2 (7.69%)	23 (14.65%)	65 (12.95%)
WEIGHT DECREASED	16 (5.02%)	9 (4.92%)	0 (0.00%)	9 (5.73%)	25 (4.98%)
WEIGHT INCREASED	7 (2.19%)	4 (2.19%)	2 (7.69%)	2 (1.27%)	11 (2.19%)
WHITE BLOOD CELL COUNT DECREASED	27 (8.46%)	18 (9.84%)	2 (7.69%)	16 (10.19%)	45 (8.96%)
METABOLISM AND NUTRITION DISORDERS					
DECREASED APPETITE	44 (13.79%)	19 (10.38%)	1 (3.85%)	18 (11.46%)	63 (12.55%)
HYPERKALAEMIA	6 (1.88%)	4 (2.19%)	2 (7.69%)	2 (1.27%)	10 (1.99%)
HYPOCALCAEMIA	8 (2.51%)	5 (2.73%)	2 (7.69%)	3 (1.91%)	13 (2.59%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS					
ARTHRALGIA	57 (17.87%)	39 (21.31%)	9 (34.62%)	30 (19.11%)	96 (19.12%)
BACK PAIN	37 (11.60%)	24 (13.11%)	4 (15.38%)	20 (12.74%)	61 (12.15%)
BONE PAIN	35 (10.97%)	15 (8.20%)	6 (23.08%)	9 (5.73%)	50 (9.96%)
MUSCULOSKELETAL CHEST PAIN	12 (3.76%)	6 (3.28%)	2 (7.69%)	4 (2.55%)	18 (3.59%)
MUSCULOSKELETAL PAIN	21 (6.58%)	14 (7.65%)	2 (7.69%)	12 (7.64%)	35 (6.97%)
MYALGIA	18 (5.64%)	6 (3.28%)	0 (0.00%)	6 (3.82%)	24 (4.78%)
PAIN IN EXTREMITY	52 (16.30%)	23 (12.57%)	3 (11.54%)	20 (12.74%)	75 (14.94%)
NERVOUS SYSTEM DISORDERS					
DIZZINESS	26 (8.15%)	12 (6.56%)	4 (15.38%)	8 (5.10%)	38 (7.57%)
DYSGEUSIA	20 (6.27%)	11 (6.01%)	4 (15.38%)	7 (4.46%)	31 (6.18%)
HEADACHE	56 (17.55%)	36 (19.67%)	10 (38.46%)	26 (16.56%)	92 (18.33%)
HYPOAESTHESIA	3 (0.94%)	5 (2.73%)	3 (11.54%)	2 (1.27%)	8 (1.59%)

POLYNEUROPATHY	16 (5.02%)	5 (2.73%)	1 (3.85%)	4 (2.55%)	21 (4.18%)
PSYCHIATRIC DISORDERS					
DEPRESSION	7 (2.19%)	8 (4.37%)	2 (7.69%)	6 (3.82%)	15 (2.99%)
INSOMNIA	31 (9.72%)	26 (14.21%)	4 (15.38%)	22 (14.01%)	57 (11.35%)
SLEEP DISORDER	13 (4.08%)	10 (5.46%)	4 (15.38%)	6 (3.82%)	23 (4.58%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS					
VULVOVAGINAL DRYNESS	4 (1.25%)	3 (1.64%)	3 (11.54%)	0 (0.00%)	7 (1.39%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS					
COUGH	53 (16.61%)	22 (12.02%)	6 (23.08%)	16 (10.19%)	75 (14.94%)
DYSPNOEA	49 (15.36%)	25 (13.66%)	4 (15.38%)	21 (13.38%)	74 (14.74%)
OROPHARYNGEAL PAIN	11 (3.45%)	7 (3.83%)	5 (19.23%)	2 (1.27%)	18 (3.59%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS					
ALOPECIA	119 (37.30%)	57 (31.15%)	5 (19.23%)	52 (33.12%)	176 (35.06%)
DRY SKIN	24 (7.52%)	15 (8.20%)	3 (11.54%)	12 (7.64%)	39 (7.77%)
ERYTHEMA	9 (2.82%)	10 (5.46%)	1 (3.85%)	9 (5.73%)	19 (3.78%)
PRURITUS	45 (14.11%)	18 (9.84%)	3 (11.54%)	15 (9.55%)	63 (12.55%)
RASH	47 (14.73%)	19 (10.38%)	2 (7.69%)	17 (10.83%)	66 (13.15%)
VASCULAR DISORDERS					
HOT FLUSH	44 (13.79%)	30 (16.39%)	11 (42.31%)	19 (12.10%)	74 (14.74%)
HYPERTENSION	36 (11.29%)	11 (6.01%)	4 (15.38%)	7 (4.46%)	47 (9.36%)

Conclusion:

Considering the broad patient population with HR-positive, HER2-negative advanced breast cancer, the overall Clinical benefit rate (CBR) of 60.8% is a convincing result and confirms the findings from previous studies. The CBR in treatment naïve patients was slightly higher than in pre-treated patients. The results were confirmed by multiple sensitivity analyses. Progression Free Survival (PFS) was also longer in Cohort A than in Cohort B including pre-treated patients. Treatment benefit was achieved for all subpopulations of this study. The combination of ribociclib and letrozole was associated with a manageable safety profile that is generally consistent with previous experience with ribociclib.

The results are in line with the data of the pivotal phase III studies MONALEESA-2, MONALEESA-3, MONALEESA-7. No new safety signals were detected and no unexpected toxicities were observed supporting the manageable tolerability profile of the treatment regimen

Date of Clinical Trial Report

09 Nov 2020