Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Ribociclib

Trial Indication(s)

Breast Cancer

Protocol Number

CLEE011ABR02

Protocol Title

An observational, retrospective, multicenter, national study of the effectiveness of ribociclib in combination with non-steroidal aromatase inhibitors in first-line treatment of Brazilian patients with HR+/HER2- advanced breast cancer

Clinical Trial Phase

IV

Phase of Drug Development

NA

Study Start/End Dates

Study start date: 23/03/2021

Study Completion date: 29/10/2021

Reason for Termination

NA

Study Design/Methodology

Observational, longitudinal (retrospective cohort), multicenter, national study aiming to evaluate the proportion of women with HR+/HER2- advanced breast cancer treated with ribociclib plus non-steroidal aromatase inhibitors who were alive and without disease progression at 1 year.

The study was conducted in 11 Brazilian sites specialized in the treatment of this condition. The study data were collected from the review of medical records by the Investigator (or designated).

The sites must have had adequate medical records to ensure robust medical record review. Therefore, a feasibility assessment was carried out at potential site prior to the study implementation to assess the adequacy of medical records and the data routinely available.

Centers

Novartis Investigative Site

Objectives:

Primary objective(s)

- Evaluate the effectiveness of first line ribociclib in combination with non-steroidal aromatase inhibitors in a Brazilian female population diagnosed with HR+/HER2- locally advanced or metastatic BC. Effectiveness will be measured by the proportion of patients alive and free of disease progression at 1 year

Secondary objective(s)

Describe the clinical and demographic characteristics of the patients included in the study

- Age (mean, median)
- Race (white, brown, black, yellow and indigenous)
- Presence of cardiac comorbidities: arterial hypertension
- Presence of endocrine comorbidities: obesity and DM2

- Diagnosis time in years
- Diagnosis stage, according to the TNM classification
- Metastasis sites (soft tissue, bone, visceral, lymph nodes, skin)
- Disease-free interval: de novo diagnosis, existing disease ≤ 12 months after end of adjuvance,> 12 months after end of adjuvance
- Previous (neo)adjuvant treatment: Chemotherapy, anastrozole, exemestane, letrozole, tamoxifen, other
- ECOG performance status: 0-5
- Evaluate the proportion of patients alive and free of progression at 6 months.
- Evaluate the proportion of patients who had disease progression at 6 months and 1 year
- Evaluate the proportion of patients who died at 6 months and 1 year
- Compare the proportions of patients alive and progression-free between treatment doses (600 mg, 400 mg, and 200 mg) at 6 months and 1 year
- Compare the proportions of patients alive and progression-free among patients with presence and absence of visceral metastasis at 1 year
- Compare the proportions of patients alive and progression-free among the patients with de novo diagnosis and those who progressed from earlier stages at 1 year
- Compare the proportions of patients alive and progression-free based on the disease- free interval (early and late recurrence) at 1 year
- Compare the proportions of patients alive and progression-free at 6 months versus 1 year
- Evaluate the proportion and cause of patients who reduced a treatment dose (from 600 mg to 400 mg or from 400 mg to 200 mg) at 6 months and 1 year
- Compare the need for dose reduction at 6 months versus 1 year
- Evaluate the frequency of dose interruption and cause, per patient, in one year.
- Evaluate the frequency and degree of severity of the following adverse events of interest: neutropenia, febrile neutropenia, increased QT interval (> 60 ms,> 480ms ≤ 500 ms, and> 500 ms), AST/ALT elevation three times greater than upper limit
- Evaluate how the patients with AE of interest were treated (ie. Dose reduction or interruption, showing the respective proportions and medications taken).

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

NA

Statistical Methods

Continuous variables were summarized as mean and standard deviation, and median and interquartile range. Discrete variables were summarized by absolute (n) and relative (%) frequencies.

Fisher's exact test of independence were used for comparisons of two or more proportions, as defined in the secondary objectives. The defined level of significance is 0.05 at two-tailed test. The measure of association between two interest groups were estimated by the relative risk, presented with the respective 95% confidence interval.

Time to event analysis as progression-free of disease (primary endpoint) and survival were also presented in Kaplan Meier curves, and incidences were presented in patient-years as well. All incidences and proportions described in as primary and secondary endpoints were presented with 95% confidence intervals.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

- Female patient ≥ 18 years of age. All the patients must have at least one year of follow-up
- Patients at an age not consistent with postmenopausal status could only participate if they had oophorectomy surgery or being on treatment with goserelin for ovarian suppression
    - Post-menopausal women defined as age ≥ 60 years old or < 60 years old and amenorrhea for 12 months or more (in the absence of chemotherapy, tamoxifen, toremifene or goserelin use for ovarian suppression)
- Confirmed diagnosis of HR+/HER2- locally advanced or metastatic BC
- Never in use of CDK 4/6i

Exclusion criteria

- Patients in menopause status other than postmenopausal (young patients must have undergone oophorectomy being on treatment with goserelin for ovarian suppression to be characterized as postmenopausal)
- Previous use, at any time, of CDK 4/6i
- The patient received any previous systemic therapy for advanced breast cancer
    - Patients who have received (neo)adjuvant therapy for breast cancer are eligible. If previous (neo) adjuvant therapy has included letrozole or anastrozole, the disease- free interval should be longer than 12 months from completion of treatment until entry in this trial

    - Patients who received ≤28 days of letrozole or anastrozole for advanced disease prior to inclusion in this trial are eligible
- Uncontrolled heart disease and/or clinically significant cardiac repolarization abnormalities

Participant Flow

Starting in March/2021, 97 patients were initially screened, to enter in the BrasiLEEira observational study. A total of 21 patients did not proceed to enrollment due to failure to comply with protocol inclusion/exclusion criteria. Overall, of the 21 patients not proceeding to enrollment after initial screening, 6 (28.57%) did not meet one of the inclusion criteria and 15 (71.42%) met one of the exclusion criteria. Data of 76 patients were collected in the study, given that the first patient was enrolled on March 23, 2021, and the last patient was enrolled on October 29, 2021.

Baseline Characteristics

Variable	Total (n=76)
Age (mean, median)	57 ± 13.2, 57 [48.8 - 65.2] (n=76)
Ethnicity — no. (%)	
White	53/76 (69.7%)
Black	8/76 (10.5%)
Brown	14/76 (18.4%)
Asian	1/76 (1.3%)
Indigenous	0/76 (0%)
Presence of cardiac comorbidities: arterial hypertension — no. (%)	26/75 (34.7%)
Presence of endocrine comorbidities: obesity — no. (%)	17/74 (23%)
Presence of endocrine comorbidities: DM2 — no. (%)	6/75 (8%)
Diagnosis time in years (mean, median)	4 ± 5, 1.6 [0.2 – 7.5] (n=68)
Diagnosis stage, according to the TNM classification — no. (%)	
Stage 0	0/76 (0%)
Stage IA	10/76 (13.2%)
Stage IB	0/76 (0%)
Stage IIA	7/76 (9.2%)
Stage IIB	7/76 (9.2%)
Stage IIIA	2/76 (2.6%)
Stage IIIB	6/76 (7.9%)
Stage IIIC	2/76 (2.6%)
Stage IV	26/76 (34.2%)
Not Available	16/76 (21.1%)
Metastasis — no. (%)	74/76 (97.4%)
TNM	
T0N0M1	2/76 (2.6%)
T1N0M0	10/76 (13.2%)
T1N0M1	1/76 (1.3%)
T1N1M0	1/76 (1.3%)
T2N0M0	6/76 (7.9%)
T2N0M1	2/76 (2.6%)
T2N1aM0	1/76 (1.3%)
T2N1M0	6/76 (7.9%)

Variable	Total (n=76)
T2N1M1	3/76 (3.9%)
T2N3aM1	1/76 (1.3%)
T2NXM1	1/76 (1.3%)
T3N1M0	1/76 (1.3%)
T3N1MX	1/76 (1.3%)
T3N2M0	1/76 (1.3%)
T3N2M1	2/76 (2.6%)
T3N3cM0	1/76 (1.3%)
T4N0M1	1/76 (1.3%)
T4N1M0	3/76 (3.9%)
T4N1M1	5/76 (6.6%)
T4N2M0	3/76 (3.9%)
T4N2M1	4/76 (5.3%)
T4N3bM0	1/76 (1.3%)
T4NXM1	1/76 (1.3%)
TXN0M0	1/76 (1.3%)
TXNXM1	2/76 (2.6%)
TXNXMX	15/76 (19.7%)
Metastasis sites — no. (%)	
1	16/74 (21.6%)
2	18/74 (24.3%)
3 or more	40/74 (54.1%)
Not Available	0/74 (0%)
Metastasis locations — no. (%)	
Unknown	26/74 (35.1%)
Soft Tissue	2/48 (4.2%)
Bone	33/48 (68.8%)
Visceral	29/48 (60.4%)
Lymph nodes	20/48 (41.7%)
Skin	3/48 (6.3%)
Breast	2/48 (4.2%)
Other	1/48 (2.1%)
Disease-free interval — no. (%)	
De novo diagnosis	26/74 (34,1%)%)
Existing disease ≤ 12 months after end of adjuvance,	19/74 (25.7%)
Existing disease > 12 months after end of adjuvance	25/74 (33.8%)
Not Available	2/76 (2.6%)

Variable	Total (n=76)
Previous (neo)adjuvant treatment — no. (%)	
Chemotherapy	34/74 (45.9%)
Anastrozole	3/72 (4.2%)
Exemestane	1/72 (1.4%)
Letrozole	1/72 (1.4%)
Tamoxifen	36/72 (50%)
Other	8/72 (11.1%)
CT Adjuvant Medication — no. (%)	
Docetaxel	5/35 (14.3%)
Paclitaxel	13/35 (37.1%)
Doxorrubicin	25/35 (71.4%)
LipossomalDox	0/35 (0%)
Gencitabine	0/35 (0%)
Vinirelbine	0/35 (0%)
Capacitabin	0/35 (0%)
Ciclofosfamide	33/35 (94.3%)
Metrotexate	4/35 (11.4%)
Fluoruracil	11/35 (31.4%)
Carboplatin	0/35 (0%)
AdMedOther	4/35 (11.4%)
Hormonal (Neo)Adjuvant Therapy — no. (%)	35/73 (47.9%)
HormonalTherapy time in years (mean, median)	3.6 ± 1.9, 3.9 [2 - 5] (n=21)
ECOG performance status — no. (%)	
0	43/69 (62.3%)
1	24/69 (34.8%)
2	1/69 (1.4%)
3	1/69 (1.4%)
4	0/69 (0%)
5 (Not Available)	7/76 (9.2%)

Primary and Secondary Outcome Result(s)

Outcomes

Outcomes	6 months	CI (95%)	12 months	CI (95%)
Proportion of patients alive and progression-free from disease	68/76 (89.5%)	89.5% [79.8% - 95.0%]	59/76 (77.6%)	77.6% [66.4% - 86.1%]
Proportion of patients who died	0/76 (0%)	-	3/76 (3.9%)	3.9% [1.0% - 11.9%]
Proportion of patients who had disease progression or died	8/76 (10.5%)	10.5% [5.0% - 20.2%]	16/76 (21.1%)	21.0% [12.9% - 32.2%]

The progression disease and doses by visit

Progression and doses change from baseline

	6 months				
	Dose reduction from 600mg to 200mg (n=6)	Dose reduction from 600mg to 400mg (n=14)	Maintained at 600mg (n=46)	Total (n=66)	p
Disease Progressed (No)	5/6 (83.3%)	14/14 (100%)	43/46 (93.5%)	62/66 (93.9%)	0.348
Disease Progressed (Yes)	1/6 (16.7%)	0/14 (0%)	3/46 (6.5%)	4/66 (6.1%)	
	12 months				
	Dose reduction from 600mg to 200mg (n=6)	Dose reduction from 600mg to 400mg (n=14)	Maintained at in 600mg (n=33)	Total (n=53)	p
Disease Progressed (No)	6/6 (100%)	14/14 (100%)	33/33 (100%)	53/53 (100%)	1
Disease Progressed (Yes)	0/6 (0%)	0/14 (0%)	0/33 (0%)	0/53 (0%)	

Adverse events - at least one event in the period of the study

Adverse Events - at least one event in the period				
	6 months	IC (95%)	12 months	IC (95%)
Neutropenia (**Appendix 16**)	51/76 (67.1%)	67.11% [55.27% - 77.2%]	52/76 (68.4%)	68.42% [56.62% - 78.34%]
Severity				
Grade 1(ANC < 1, 5x109L)	6/76 (7.9%)	7.89% [3.25% - 17%]	7/76 (9.2%)	9.21% [4.1% - 18.62%]
Grade 2(ANC 1, 5 - 1, 0 x109L)	20/76 (26.3%)	26.32% [17.18% - 37.88%]	20/76 (26.3%)	26.32% [17.18% - 37.88%]
Grade 3(ANC 1, 0 - 0, 5 x109L)	29/76 (38.2%)	38.16% [27.47% - 50.06%]	30/76 (39.5%)	39.47% [28.65% - 51.37%]
Grade 4(ANC < 0, 5 x109L)	3/76 (3.9%)	3.95% [1.03% - 11.88%]	3/76 (3.9%)	3.95% [1.03% - 11.88%]
Febrile	No events	-	1/76 (1.3%)	1.32% [0.07% - 8.11%]
Severity				
Grade 3 (ANC <1x109 L and >38,3ºC or 38ºC more than 1 hour)	-		1/1 (100%)	1.32% [0.07% - 8.11%]
Grade 4 Life threatening	-		0/1 (0%)	-
Prolonged QT interval	1/76 (1.3%)	1.32% [0.07% - 8.11%]	1/76 (1.3%)	1.32% [0.07% - 8.11%]
Severity				
Increased QT interval > 60 ms	0/1 (0%)	-	0/1 (0%)	-
Increased QT interval > 480ms ≤ 500 ms	1/76 (1.3%)	1.32% [0.07% - 8.11%]	1/76 (1.3%)	1.32% [0.07% - 8.11%]
Increased QT interval > 500 ms	0/1 (0%)	-	0/1 (0%)	-
Aspartate aminotransferase increase (AST) > 3x ULN observed in the period	4/76 (5.3%)	5.26% [1.7% - 13.64%]	4/76 (5.3%)	5.26% [1.7% - 13.64%]
Alanine aminotransferase increase (ALT) > 3x ULN observed in the period	3/76 (3.9%)	3.95% [1.03% - 11.88%]	5/76 (6.6%)	6.58% [2.45% - 15.34%]

Adverse events – pattern of treatment

Pattern of the treatment of AE of interest (ie. Ribociclib dose reduction or interruption showing the respective proportions and medications taken).	6 months	IC (95%)	12 months	IC (95%)
Neutropenia	51/76 (67.1%)	67.11% [55.27% - 77.2%]	52/76 (68.4%)	68.42% [56.62% - 78.34%]
None	26/51 (51%)	-	26/52 (50%)	-
Temporary interruption of Ribociclib	24/51 (47.1%)	-	24/52 (46.2%)	-
*Period (total days; mean)*Patient 0104004 with missing days values*	10.6 ± 7.3 (n=23)		12.2 ± 8.6 (n=23)	
Lowering of Ribociclib dose	9/51 (17.6%)	-	10/52 (19.2%)	-
Dose (mg/day)*Patients 0104005 and 0105003 with two changes of doses.				
400	9/9 (100%)	-	10/10 (100%)	-
200	2/9 (22.2%)	-	2/10 (20%)	-
Definitive interruption of Ribociclib	0/51 (0%)	-	0/52 (0%)	-
Other	0/51 (0%)	-	0/52 (0%)	-
Febrile	0/76 (0%)	-	1/76 (1.3%)	1.32% [0.07% - 8.11%]
None	-	-	0/1 (0%)	-
Temporary interruption of Ribociclib	-	-	0/1 (0%)	-
Lowering of Ribociclib dose	-	-	0/1 (0%)	-
Definitive interruption of Ribociclib	-	-	0/1 (0%)	-
Other [1]	-	-	1/1 (100%)	
Prolonged QT interval	1/76 (1.3%)	1.32% [0.07% - 8.11%]	1/76 (1.3%)	1.32% [0.07% - 8.11%]
None	0/1 (0%)	-	0/1 (0%)	-
Temporary interruption of Ribociclib	1/1 (100%)	-	1/1 (100%)	-
Period (total days; mean)	18 (n=1)		18 (n=1)	
Lowering of Ribociclib dose	0/1 (0%)	-	0/1 (0%)	-
Definitive interruption of Ribociclib	0/1 (0%)	-	0/1 (0%)	-

Pattern of the treatment of AE of interest (ie. Ribociclib dose reduction or interruption showing the respective proportions and medications taken).	6 months	IC (95%)	12 months	IC (95%)
Other	0/1 (0%)	-	0/1 (0%)	-
AspartateAE	4/76 (5.3%)	5.26% [1.7% - 13.64%]	4/76 (5.3%)	5.26% [1.7% - 13.64%]
None	0/4 (0%)		0/4 (0%)	
Temporary interruption of Ribociclib	3/4 (75%)	-	3/4 (75%)	-
*Period (total days; mean)*Patient 0102004 without information about days of interruption in the visits*	11 ± 2.8 (n=2)		11 ± 2.8 (n=2)	
Lowering of Ribociclib dose	1/4 (25%)	-	1/4 (25%)	-
Dose (mg/day)				
400	1/1 (100%)		1/1 (100%)	-
200	0/1 (0%)		0/1 (0%)	
Definitive interruption of Ribociclib	1/4 (25%)	-	1/4 (25%)	-
Other	1/4 (25%)	-	1/4 (25%)	-
AlanineAE	3/76 (3.9%)	3.95% [1.03% - 11.88%]	5/76 (6.6%)	6.58% [2.45% - 15.34%]
None	0/3 (0%)		0/5 (0%)	
Temporary interruption of Ribociclib	2/3 (66.7%)	-	3/5 (60%)	-
*Period (total days; mean)*Patient 0102004 without information about days of interruption in the visits*	7 (n=1)		28 ± 29.7 (n=2)	
Lowering of Ribociclib dose	1/3 (33.3%)	-	1/5 (20%)	-
Dose (mg/day)				
400	0/1 (0%)	-	0/1 (0%)	-
200	1/1 (100%)	-	1/1 (100%)	-
Definitive interruption of Ribociclib	1/3 (33.3%)	-	2/5 (40%)	-
Pattern of the treatment of AE of interest (ie. Ribociclib dose reduction or interruption showing the respective proportions and medications taken).	6 months	IC (95%)	12 months	IC (95%)
Other	0/3 (0%)	-	0/5 (0%)	-

1: hospitalized for treatment of febrile neutropenia by chemotherapy

Safety Results
Refer to Adverse events tables in the outcomes section

Other Relevant Findings
Not applicable.

Conclusion
This real-world evidence suggested the same benefit of adding ribociclib to ET in progression-free survival among patients receiving first-line therapy and were consistent with the findings in the clinical trials. The therapy was well tolerated with similar dose lowering and treatment discontinuation rates due to toxicity compared to pivotal RCTs. It is nurturing to witness drug tolerability, and effectiveness reproduced in real-world patients.

Date of Clinical Study Report
10 August 2022