

Real-World Evidence of Ribociclib Plus Aromatase Inhibitors as First-Line Treatment in Advanced Breast Cancer: The BrasiLEEira Study

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ABSTRACT

PURPOSE Cyclin inhibitors plus endocrine therapy represent the reference standard for hormone receptor–positive (HR+)/human epidermal growth factor receptor 2–negative (HER2–) locally advanced or metastatic breast cancer (ABC). Efficacy results on hard end points such as overall survival come from well-designed randomized clinical trials (RCTs). However, a limitation of RCTs is the low external results validity, and their extrapolation to a broader population may not be appropriate. Real-world studies can overcome these limitations, also increasing the reliability of RCTs.

MATERIALS AND METHODS The BrasiLEEira was an observational, longitudinal, retrospective, multi-center study to evaluate the effectiveness and safety of ribociclib plus non-steroidal aromatase inhibitors in Brazilian women age 18 years or older with HR+/HER2– ABC. The study was approved by the institutional review boards of all 11 hospitals. Data were collected anonymously from medical records using an electronic case report form designed by an independent academic research organization, which conducted the study considering all recommendations of international guidelines. The primary end point was 1-year progression-free survival (PFS) rate. Secondary end points included mortality, dose reduction, and safety.

RESULTS The mean age of 76 patients was 57 years, and 28.9% were Black/Brown. The most prevalent comorbidity was arterial hypertension (34.7%). About 26.0% had endocrine-resistant disease, and 54.1% had more than three metastatic sites. The PFS rate was 77.6%. Three patients died (3.9%). Dose reductions occurred in 37.7% of patients. The most common adverse event was neutropenia (68.4%).

CONCLUSION The high-quality evidence from the BrasiLEEira study corroborates the RCTs' findings, expanding its validity to a broader spectrum and underrepresented population who may benefit from ribociclib treatment.

ACCOMPANYING CONTENT

 Appendix

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INTRODUCTION

Breast cancer is the most common type of cancer worldwide¹ and the most frequent neoplasm in Brazil after nonmelanoma skin cancer, representing 10.5% of patients.² According to National Cancer Institute estimates, there will be 73,610 new patients of breast cancer in Brazil in 2023.²

Hormone receptor–positive (HR+)+/human epidermal growth factor receptor 2–negative (HER2–) is the most common subtype of breast cancer, representing 72.7% of

patients in any stage³ and 58% of advanced patients.⁴ Associating cyclin-dependent kinase (CDK) 4/6 inhibitors with endocrine therapy is the gold standard treatment for this subtype of breast cancer, improving progression-free and overall survival compared with single-agent hormone therapy, having been recognized in national^{5,6} and international guidelines.^{7,8}

Ribociclib is a CDK 4/6 inhibitor whose efficacy and safety have been proven through a robust series of phase III randomized clinical trials (RCTs) called MONALEESA,

CONTEXT

Key Objective

Is first-line ribociclib effective in treating women with locally advanced or metastatic hormone receptor–positive/human epidermal growth factor receptor 2–negative breast cancer in real-world practice?

Knowledge Generated

Ribociclib is a cyclin-dependent kinase 4/6 inhibitor whose efficacy and safety have been proven through a robust series of phase III randomized clinical trials (RCTs) called MONALEESA. Knowledge generated by the BrasiLEEira study shows that progression-free survival at 12 months was 77.6% among included patients, a rate higher than that in the MONALEESA-2 (74.53%) and MONALEESA-7 trials (72.7%). The 1-year mortality rate in the BrasiLEEira (3.95%) was similar to that in the MONALEESA-7 (3%), with no causality due to adverse events.

Relevance

The relevance of high-quality evidence from the BrasiLEEira study makes an important contribution to the body of consistent scientific evidence on ribociclib, increasing confidence in the effect size observed in RCTs and expanding its validity to a broader spectrum of patients who may benefit from ribociclib treatment.

which consists of three pivotal studies: MONALEESA-2,^{9–11} MONALEESA-7,^{12–14} and MONALEESA-3.^{15,16} On the basis of evidence from these studies and the current state of the art, ribociclib is the only representative of its class that has shown clinically and statistically significant improvements in patients with de novo diagnosis and endocrine therapy sensitive first-line treatment. It is estimated to reduce the risk of death between 24%¹¹ and 29%,¹³ with median overall survival reaching 63.9 months.¹¹ In endocrine therapy resistance and second-line treatment, either ribociclib¹⁶ or abemaciclib¹⁷ showed clinically and statistically significant overall survival gains of similar magnitudes.

Although RCTs are the gold standard for interventional studies,¹⁸ they could have limitations such as low external validity because of inclusion and exclusion criteria and regulated follow-up protocols, so generalizations of the findings outside the study population may be invalid.^{19,20} Consequently, it is a challenge to extrapolate drug efficacy to drug effectiveness in clinical practice.

Real-world evidence, that is, data collected outside the RCT context,¹⁸ could theoretically be used to estimate the effectiveness of novel or existing drugs in clinical practice. Thus, it could support RCT evidence and broaden the population that can benefit from treatment. However, scientific rigor is crucial to overcoming the limitations and potential bias of non-RCT methodologies, such as observational studies.

In this context, the aim of this study was to evaluate the effectiveness and safety of ribociclib in patients diagnosed with locally advanced or metastatic HR+/HER2–breast cancer who were treated at 11 private institutions in Brazil.

MATERIALS AND METHODS

Study Design

This was an observational, longitudinal, retrospective, multicenter cohort study designed to evaluate the effectiveness and safety of ribociclib plus nonsteroidal aromatase inhibitors in Brazilian women with advanced HR+/HER2–breast cancer. This study was conducted in accordance with the Declaration of Helsinki and approved by the institutional review boards of all 11 hospitals (approval number: 4.348.894, approved on October 20, 2020). Owing to the retrospective nature of data collection, the informed consent was not mandatory.

Setting and Study Population

The inclusion criteria were female patients age 18 years or older, with locally advanced or metastatic HR+/HER2–breast cancer and with at least 1 year of follow-up after having started treatment with ribociclib. Postmenopausal status was considered age ≥60 years or <60 years with ≥12 months of amenorrhea (in the absence of chemotherapy, tamoxifen, toremifene, or goserelin therapy for ovarian suppression). Premenopausal patients could only be enrolled if they had undergone a bilateral oophorectomy or received goserelin to suppress ovarian function concomitant with endocrine therapy.

The exclusion criteria were premenopausal patients who had not undergone bilateral oophorectomy or concomitant goserelin therapy for ovarian suppression; previous use, at any time, of CDK 4/6 inhibitors; uncontrolled heart disease and/or clinically significant cardiac repolarization abnormalities; and any previous systemic therapy for advanced breast cancer,

except (1) patients who received (neo)adjuvant therapy for breast cancer, including previous (neo)adjuvant therapy with letrozole or anastrozole and (2) patients who received ≤ 28 days of letrozole or anastrozole for advanced disease before inclusion in this trial. Complete eligibility criteria and the reasons for exclusion are shown in Appendix [Figure A1](#).

Data Source and Collected Variables

The data of interest were collected anonymously from electronic medical records at each institution by the investigator or a person formally designated by him/her using an electronic case report form (BrasILEEira version 1.2.6, developed by NovaTela Solutions [São Paulo, Brazil]),²¹ which was provided to participating sites by the designated independent academic research organization. Secondary data included preexisting clinical and treatment-related information previously collected by the institution during routine care (age, race, cardiac comorbidities, endocrine comorbidities, time since diagnosis [years], TNM stage,²² metastasis sites, disease-free interval, previous [neo]adjuvant treatment, and Eastern Cooperative Oncology Group²³ performance status).

A total of five data collection time points were defined. The first was the date of initiation of ribociclib treatment, when all baseline characteristics were collected. Follow-up visits occurred at 3, 6, 9, and 12 months after the beginning of treatment.

Quality Control

To ensure data quality and avoid transcription errors, automated queries were created for each field according to study-defined format data rules and reference values on the basis of data dictionary. Manual queries were issued by a clinical research association during on-site or remote monitoring visits.

All security parameters recommended in international guidelines regarding the use of electronic case report forms were built into the system. Thus, site users could directly edit the forms through the system, and any data changes made by investigators and/or their teams and the reasons for those changes were recorded in the system, ensuring data veracity and quality. If an item could not be changed via the system, the user could request correction through a data clarification form (IT OC 021), which was sent to the development team, who made the necessary changes in the database. Manual data cleaning rounds were performed weekly and at the end of study, when recruitment ended and all patients ($n = 97$) had been verified. The database was locked on November 12, 2021.

Description of Intervention

Ribociclib was administered orally at a full dose of 600 mg once daily (three tablets of 200 mg) for 21 days, followed by 7 days without medication. A total of two dose reductions were allowed: ribociclib 400 mg once daily or 200 mg once

daily, orally, for 21 days, followed by 7 days without medication. Ribociclib was administered with concurrent letrozole at a fixed continuous dose of 2.5 mg orally once daily.

Study End Points and Definitions

The primary end point was progression-free survival (PFS) rate at 1 year. Disease progression was defined as at least a 20% increase in the sum of the diameters of all measured targets, with the reference being the lowest sum of the diameters of all target lesions recorded on or after baseline. In addition to a relative increase of 20%, the sum also had to include an absolute increase of at least 5 mm. The secondary end points included disease progression at 6 and 12 months, mortality at 6 and 12 months, dose reduction or discontinuation, and safety at 12 months.

Sample Size

A sample of 150 patients was expected, considering 75% PFS at 1 year. With a 95% CI, the margin of error for PFS was estimated at 6.9%. However, since the sample included only 76 patients, the sample size premises were changed accordingly, resulting in a 9.8% precision margin for the primary outcome.

Statistical Analysis

PFS and mortality at 1 year were presented as Kaplan-Meier curve, and 1-year incidences were described with 95% CI on the basis of Poisson regression with robust variance estimation adjusted for individual exposure time. If a disease progression event or death was reported with no date, it was assumed to have occurred at the final visit. No other imputation methods were used.

Dose changes within 3 months and PFS within 1 year were compared using the log-rank test. Additional exploratory analysis of the association between baseline disease characteristics (disease-free interval and visceral metastasis) and disease progression was presented as frequency tables and compared using Fisher exact tests. A significance level of 5% was used for all statistical tests. All analyses were performed in R (R Core Team, Vienna, Austria).

RESULTS

Between March 2021 and October 28, 2021, 97 patients were initially screened, of whom 21 did not meet the eligibility criteria, and data from 76 patients from 11 Brazilian centers were analyzed.

Patient Characteristics

The mean patient age was 57 (standard deviation, 13) years. A total of 28.9% were Black or Brown patients, and 34.2% had de novo metastatic breast cancer. The most prevalent comorbidity was systemic arterial hypertension (34.7%). Approximately 26.0% had endocrine-resistant disease

(relapse on or within 12 months after the end of adjuvant therapy). The patients had similar rates of bone and visceral metastasis, and 54.1% had more than three metastatic sites. Tamoxifen was the most common adjuvant treatment (50.0%). The complete population's characteristics are summarized in [Table 1](#).

Outcome Data

The PFS at 1 year was 77.6% (95% CI, 66.4 to 86.1).

Sixteen disease progression events occurred within 12 months, and half of these events (8 of 16) occurred within 6 months. Three patients died, all between 6 and 12 months. Disease progression and mortality rates at 12 months were 21.1% and 3.9%, respectively. [Table 2](#) summarizes these findings.

The Kaplan-Meier curves for disease progression and death within 1 year are shown in [Figures 1](#) and [2](#).

Association Between Disease Progression and Dose Reduction

There was no significant association between dose reduction and disease progression, (log-rank test, $P = .483$; Appendix [Fig A2](#)).

Association Between Disease Progression, Baseline Visceral Metastasis, and Disease-Free Interval

Appendix [Table A1](#) shows the main results for PFS rate at 12 months. There were no significant differences in PFS between those with and without baseline visceral metastasis or a disease-free interval.

Ribociclib Dose Reduction

At least one dose reduction occurred in 37.7% of patients; three patients discontinued treatment because of adverse events (Appendix [Table A2](#)).

Adverse Events

The adverse event data are summarized in Appendix [Table A3](#). The most common adverse event was neutropenia in 52 patients (67.1% at 6 months and 68.4% at 12 months, cumulatively). The most common grade 3 toxicity was neutropenia in 39.5% of patients. One patient had febrile neutropenia and another had a prolonged QT interval (>480 ms and <500 ms). AST increased in four patients, and ALT increased in five others within 1 year. More details about adverse event severity are shown in Appendix [Table A3](#).

Appendix [Table A4](#) shows the treatment pattern for all adverse events at 6 months and 1 year, considering at least one event per patient during the period.

TABLE 1. Clinical and Demographic Characteristics of the Patients

Variable	Total (N = 76)
Age (mean, median)	57 ± 13.2, 57 [48.8-65.2] (N = 76)
Race, No. (%)	
White	53/76 (69.7)
Black	8/76 (10.5)
Mixed	14/76 (18.4)
Asian	1/76 (1.3)
Indigenous	0/76 (0)
Cardiac comorbidities: arterial hypertension, No. (%)	26/75 (34.7)
Endocrine comorbidities: obesity, No. (%)	17/74 (23.0)
Endocrine comorbidities: DM2, No. (%)	6/75 (8.0)
Time since diagnosis in years (mean, median)	4 ± 5, 1.6 [0.2-7.5] (n = 68)
Initial diagnosis stage, according to the TNM classification, No. (%)	
IA	10/76 (13.2)
IB	0/76 (0)
IIA	7/76 (9.2)
IIB	7/76 (9.2)
IIIA	2/76 (2.6)
IIIB	6/76 (7.9)
IIIC	2/76 (2.6)
IV	26/76 (34.2)
Not available	16/76 (21.1)
Metastasis, No. (%)	74/76 (97.4)
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 adjuvant therapy	19/74 (25.7)
Existing disease >12 months after end of adjuvant therapy	25/74 (33.8)
Not available	2/76 (2.6)
Previous (neo)adjuvant treatment, No. (%)	
Chemotherapy	34/74 (45.9)
Anastrozole	3/72 (4.2)
Exemestane	1/72 (1.4)

(continued on following page)

TABLE 1. Clinical and Demographic Characteristics of the Patients (continued)

Variable	Total (N = 76)
Letrozole	1/72 (1.4)
Tamoxifen	36/72 (50.0)
Other	8/72 (11.1)
Adjuvant CT medication, No. (%)	
Docetaxel	5/35 (14.3)
Paclitaxel	13/35 (37.1)
Doxorubicin	25/35 (71.4)
Cyclophosphamide	33/35 (94.3)
Methotrexate	4/35 (11.4)
Fluorouracil	11/35 (31.4)
Other	4/35 (11.4)
Hormonal (neo)adjuvant therapy, No. (%)	35/73 (47.9)
Duration of adjuvant endocrine therapy 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)
Not available	7/76 (9.2)

Abbreviations: CT, chemotherapy; DM2, diabetes mellitus 2; ECOG, Eastern Cooperative Oncology Group.

DISCUSSION

The BrasiLEEira results corroborate those of pivotal MONALEESA first-line RCTs regarding the efficacy and safety of ribociclib plus aromatase inhibitors. The study demonstrates the effectiveness and safety of ribociclib in a real-world setting of Brazilian patients with HR+/HER2– advanced breast cancer with a higher rate of PFS at 12 months than in the MONALEESA-2⁹⁻¹¹ and MONALEESA-7¹² trials (77.6%, 74.53%, and 72.7%, respectively). The 1-year mortality rate in the BrasiLEEira (3.95%) was similar to that in the MONALEESA-7¹³ (3%), with no causality due to adverse

event. More importantly, the BrasiLEEira population's clinical and demographic characteristics were much broader and indicated worse prognosis than those in the MONALEESA series, which increases external validity.

It is noteworthy that the included population had disease variables associated with worse prognosis: 54.1% of the BrasiLEEira population had ≥3 metastatic sites, compared with 34.1% and 35% in MONALEESA-2⁹⁻¹¹ and MONALEESA-7,¹² respectively. BrasiLEEira had a higher percentage of patients resistant to endocrine therapy (25.7%) than MONALEESA-2⁹⁻¹¹ or MONALEESA-7¹² (1.2% and 7%, respectively). Variables such as de novo diagnosis, (neo)adjuvant treatment pattern, and Eastern Cooperative Oncology Group performance status and bone metastases were similar between the populations of BrasiLEEira and the MONALEESA series.

In addition, characterizing the population in terms of comorbidities is important for understanding how they can influence treatment, especially because they are poorly reported in trials.²⁴ In the BrasiLEEira study, 34.7% of the patients had arterial hypertension, 23% were obese, and 8% had diabetes.

Another important aspect of the BrasiLEEira study was its greater racial diversity. In BrasiLEEira, 28.9% of the population was Black or Brown, compared with 3% in the MONALEESA-2⁹⁻¹¹ and MONALEESA-7¹² trials, which further strengthens the study's findings. There is a worldwide effort to increase racial diversity in clinical trials, which is reflected in a recent initiative by the US National Academies of Sciences, Engineering, and Medicine.²⁵ Such initiatives are necessary because different population subgroups may have pharmacogenomic differences that can interfere with safety or effectiveness²⁵ and indicate those who will not benefit from treatment. Although these efforts are not yet reflected in the majority of RCTs, real-world evidence must incorporate this perspective to determine racial influence on the results, especially in racially diverse countries such as Brazil.

To the best of our knowledge, there is currently only one published real-world study on CDK 4/6 inhibitors in Brazil. Recently, Queiroz et al²⁶ retrospectively analyzed data from

TABLE 2. Summary of Outcome Data

Outcome	6 Months	12 Months	Event Rate per 100 Patient-Years (95% CI)
Death, No. (%)	0/76 (0)	3/76 (3.9)	3.9 (1.26 to 12.1)
Disease progression, No. (%)	8/76 (10.5)	16/76 (21.1)	20.8 (12.7 to 34.0)
Proportion of PFS, No. (%)	68/76 (89.5)	59/76 (77.6)	—
95% CI	79.8 to 95.0	66.4 to 86.1	—
Proportion of patients who died, No. (%)	0/76 (0)	3/76 (3.9)	—
95% CI	—	1.0 to 11.9	—
Proportion of patients who died or had disease progression, No. (%)	8/76 (10.5)	16/76 (21.1)	—
95% CI	5.0 to 20.2	12.9 to 32.2	—

Abbreviation: PFS, progression-free survival.

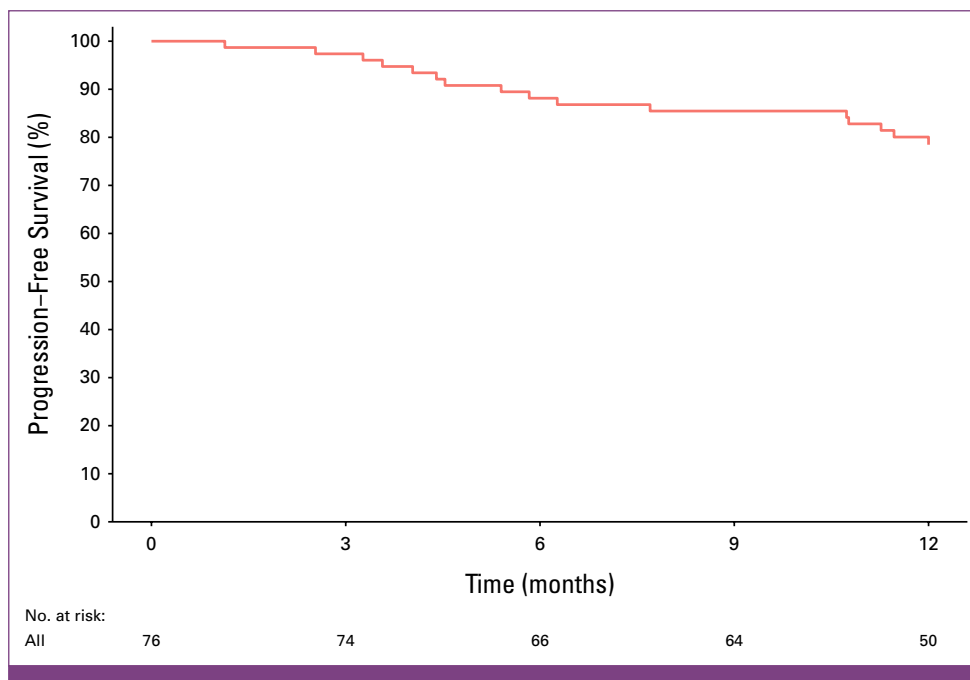


FIG 1. One-year progression-free survival.

patients with confirmed HR+/HER2 metastatic breast cancer in a single institution who were treated with endocrine therapy in combination with ribociclib, palbociclib, or abemaciclib. In an analysis restricted to patients in first-line treatment, ribociclib was superior in PFS length. In the context of other countries, other real-world evidence studies

corroborate the findings of ribociclib efficacy, demonstrating its effectiveness. Wong et al. demonstrated a longer PFS than the MONALEESA-2 trial (>36.5 vs. 25.3 months).²⁷ The CompleEment-1 study provides further real-world evidence about ribociclib first-line treatment²⁸: in a cohort of 3,246 patients with a median follow-up 25.4 months, the median

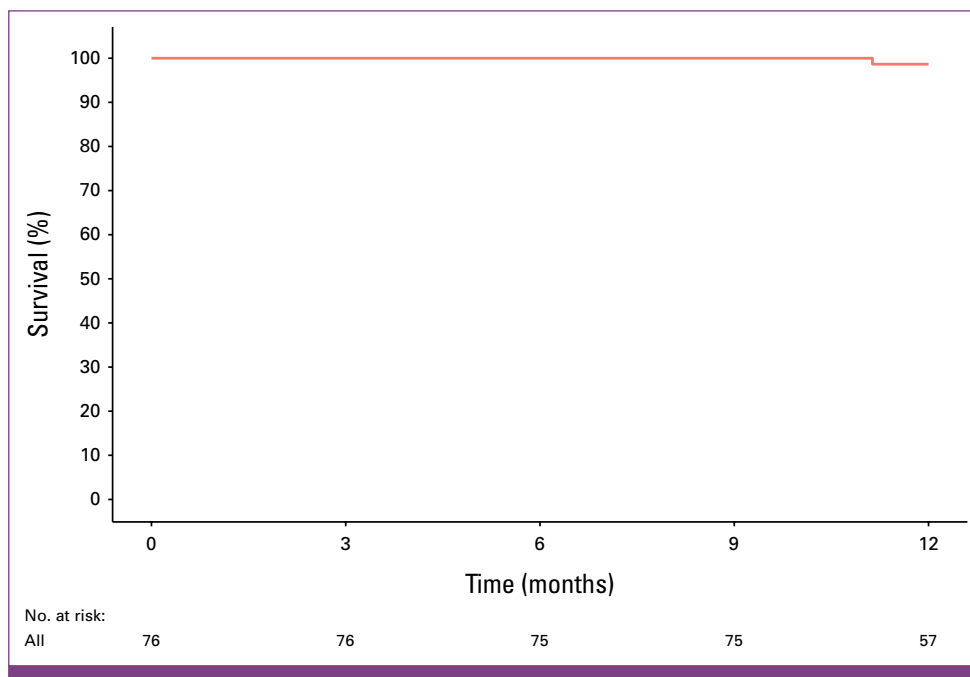


FIG 2. One-year overall survival.

PFS was 26.7 months (95% CI, 24.8 to 30.1) and the median time to progression was 27.1 months (95% CI, 25.7 to indeterminate). That population included participants with uncommon characteristics for ribociclib RCTs, such as men with breast cancer and patients with cerebral metastasis. Taken together, this real-world evidence increases the reliability of ribociclib and can facilitate clinical decision making.

Regarding safety, the pattern and frequency of adverse events were similar to those in the MONALEESA series. Neutropenia was the most frequent event, although febrile neutropenia was rare, occurring only once in the BrasiLEEira study. Similarly, increased QT interval (>480 ms and <500 ms) was more infrequent than in the MONALEESA series, also occurring in only one patient.

The main strength of the BrasiLEEira study is its methodological rigor since it followed standards generally applied in pharmaceutical industry RCTs. All research questions, eligibility criteria, and analyses were defined a priori in the Novartis study protocol. The study was approved by the research ethics committees of all 11 institutions. An independent academic research organization was hired to independently conduct the study and analyze the results. An electronic case report form was developed specifically for the study, and all security measures recommended by international guidelines for electronic case report forms were built into the system, including the recording of any data changes and their reason. Automated queries created by the system and patient monitoring during the study ensured data consistency, accuracy, veracity, and quality. Data from 100%

of patients were monitored, ensuring that they were entered into the system in accordance with what was recorded in the medical records.

The study's main limitations included its small sample size and surrogate primary outcome. Although it was expected to include 150 patients, it was conducted during the COVID-19 pandemic and thus involved challenges regarding priorities and human resources for identifying and inputting medical record data within the recruitment window. Because the main source of patients was the Novartis early access program, many patients used ribociclib in association with fulvestrant, which was excluded from the analysis. Defining the primary outcome as a discrete variable was justified by the short treatment period since the ribociclib early access program dates from 2018. Thus, considering that more than half of the patients are still alive and progression free, defining the primary outcome as a continuous variable would have resulted in an indeterminate median PFS, which would be uninformative. Furthermore, although time points were defined for the analyses, obtaining the exact date of a progression event is a challenge and could thus bias median PFS estimates, which may underestimate ribociclib's performance in real-world settings.

In conclusion, the high-quality evidence from the BrasiLEEira study makes an important contribution to the body of consistent scientific evidence on ribociclib, increasing confidence in the effect size observed in RCTs and expanding its validity to a broader spectrum of patients who may benefit from ribociclib treatment.

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DATA SHARING STATEMENT

All relevant data are within the paper and its Supplementary file.

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APPENDIX

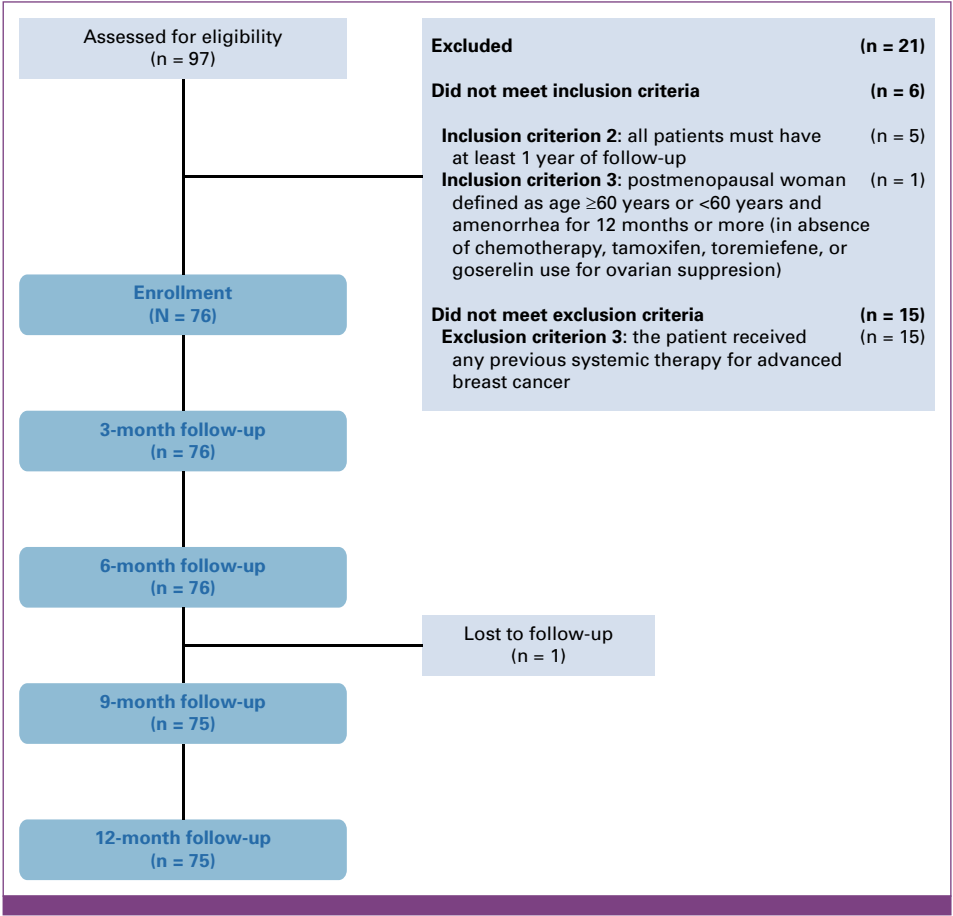


FIG A1. BrasiLEEira flowchart.

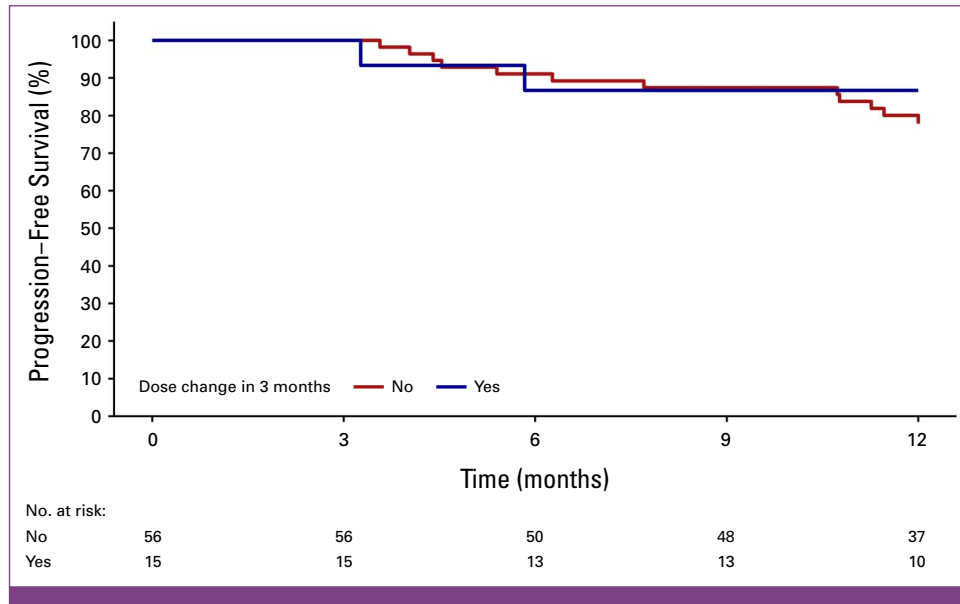


FIG A2. Association of disease progression with dose change over time.

TABLE A1. Results According to PFS at 12 months

12 Months Follow-Up				
Evaluation at First Drug Administration	Total (N = 76), n (%)	PFS, No. (%)	Relative Risk (95% CI)	P
Visceral metastasis				
No	45/74 (60.8)	35/45 (77.8)	1	
Yes	29/74 (39.2)	22/29 (75.9)	1.00 (0.80 to 1.30)	1
Disease-free interval				
De novo diagnosis	30/74 (40.5)	22/30 (73.3)	1	
Earlier stages	44/74 (59.5)	36/44 (81.8)	1.12 (0.86 to 1.44)	.40
Disease-free interval				
Early recurrence	19/44 (43.2)	15/19 (78.9)	1	
Late recurrence	25/44 (56.8)	21/25 (84)	1.06 (0.80 to 1.42)	.71

Abbreviation: PFS, progression-free survival.

TABLE A2. Daily Dose of Ribociclib

Dose	Baseline, No. (%)	6 Months, No. (%)	12 Months, No. (%)
600 mg once daily	76/76 (100)	46/66 (69.7)	33/53 (62.3)
400 mg once daily	0/76 (0)	14/66 (21.2)	14/53 (26.4)
200 mg once daily	0/76 (0)	6/66 (9.1)	6/53 (11.3)
Not available	0/76 (0)	10/76 (13.2)	23/76 (30.3)

TABLE A3. Adverse Events—At Least One Event During the Study Period

Adverse Event	6 Months, No. (%)	95% CI	12 Months, No. (%)	95% CI
Neutropenia	51/76 (67.1)	67.11 (55.27 to 77.2)	52/76 (68.4)	68.42 (56.62 to 78.34)
Severity				
Grade 1 (ANC $<1.5 \times 10^9$ L)	6/76 (7.9)	7.89 (3.25 to 17)	7/76 (9.2)	9.21 (4.1 to 18.62)
Grade 2 (ANC $1.5\text{--}1.0 \times 10^9$ L)	20/76 (26.3)	26.32 (17.18 to 37.88)	20/76 (26.3)	26.32 (17.18 to 37.88)
Grade 3 (ANC $1.0\text{--}0.5 \times 10^9$ L)	29/76 (38.2)	38.16 (27.47 to 50.06)	30/76 (39.5)	39.47 (28.65 to 51.37)
Grade 4 (ANC $<0.5 \times 10^9$ L)	3/76 (3.9)	3.95 (1.03 to 11.88)	3/76 (3.9)	3.95 (1.03 to 11.88)
Febrile	No events	—	1/76 (1.3)	1.32 (0.07 to 8.11)
Severity				
Grade 3 (ANC $<1 \times 10^9$ L and $>38.3^\circ\text{C}$ or 38°C more than 1 hour)	—		1/1 (100)	1.32 (0.07 to 8.11)
Grade 4 life-threatening	—		0/1 (0)	—
Prolonged QT interval	1/76 (1.3)	1.32 (0.07 to 8.11)	1/76 (1.3)	1.32 (0.07 to 8.11)
Severity				
Increased QT interval >60 ms	0/1 (0)	—	0/1 (0)	—
Increased QT interval >480 ms ≤ 500 ms	1/76 (1.3)	1.32 (0.07 to 8.11)	1/76 (1.3)	1.32 (0.07 to 8.11)
Increased QT interval >500 ms	0/1 (0)	—	0/1 (0)	—
Increased AST $>3 \times$ ULN observed in the period	4/76 (5.3)	5.26 (1.7 to 13.64)	4/76 (5.3)	5.26 (1.7 to 13.64)
Increased ALT $>3 \times$ ULN observed in the period	3/76 (3.9)	3.95 (1.03 to 11.88)	5/76 (6.6)	6.58 (2.45 to 15.34)

Abbreviations: ANC, absolute neutrophil count; ULN, upper limit of normal.

TABLE A4. Adverse Events—Treatment Pattern

Treatment Pattern for Adverse Events of Interest (ie, ribociclib dose reduction or interruption, showing the respective proportions and medications taken)	6 Months, No. (%)	95% CI	12 Months, No. (%)	95% CI
Neutropenia	51/76 (67.1)	67.11 (55.27 to 77.2)	52/76 (68.4)	68.42 (56.62 to 78.34)
None	26/51 (51)	—	26/52 (50)	—
Temporary ribociclib interruption	24/51 (47.1)	—	24/52 (46.2)	—
<i>Period (total days; mean) *Patient 0104004 with missing days values</i>	10.6 ± 7.3 (n = 23)		12.2 ± 8.6 (n = 23)	
Ribociclib dose reduction	9/51 (17.6)	—	10/52 (19.2)	—
<i>Dose (mg/day) *Patients 0104005 and 0105003 had two dose changes</i>				
400 once daily	9/9 (100)	—	10/10 (100)	—
200 once daily	2/9 (22.2)	—	2/10 (20)	—
Definitive ribociclib interruption	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 to 8.11)
None	—	—	0/1 (0)	—
Temporary ribociclib interruption	—	—	0/1 (0)	—
Ribociclib dose reduction	—	—	0/1 (0)	—
Definitive ribociclib interruption	—	—	0/1 (0)	—
Other ¹	—	—	1/1 (100)	—
Prolonged QT interval	1/76 (1.3)	1.32 (0.07 to 8.11)	1/76 (1.3)	1.32 (0.07 to 8.11)
None	0/1 (0)	—	0/1 (0)	—
Temporary ribociclib interruption	1/1 (100)	—	1/1 (100)	—
<i>Period (total days; mean)</i>	18 (n = 1)		18 (n = 1)	
Ribociclib dose reduction	0/1 (0)	—	0/1 (0)	—
Definitive ribociclib interruption	0/1 (0)	—	0/1 (0)	—
Other	0/1 (0)	—	0/1 (0)	—
Increased AST event	4/76 (5.3)	5.26 (1.7 to 13.64)	4/76 (5.3)	5.26 (1.7 to 13.64)
None	0/4 (0)	—	0/4 (0)	—
Temporary ribociclib interruption	3/4 (75)	—	3/4 (75)	—
<i>Period (total days; mean) *Patient 0102004 without information about days of interruption in the visits</i>	11 ± 2.8 (n = 2)		11 ± 2.8 (n = 2)	
Ribociclib dose reduction	1/4 (25)	—	1/4 (25)	—
<i>Dose (mg/day)</i>				
400 once daily	1/1 (100)	—	1/1 (100)	—
200 once daily	0/1 (0)	—	0/1 (0)	—
Definitive ribociclib interruption	1/4 (25)	—	1/4 (25)	—
Other	1/4 (25)	—	1/4 (25)	—
Increased ALT event	3/76 (3.9)	3.95 (1.03 to 11.88)	5/76 (6.6)	6.58 (2.45 to 15.34)
None	0/3 (0)	—	0/5 (0)	—
Temporary ribociclib interruption	2/3 (66.7)	—	3/5 (60)	—
<i>Period (total days; mean) *Patient 0102004 without information about days of interruption in the visits</i>	7 (n = 1)		28 ± 29.7 (n = 2)	
Ribociclib dose reduction	1/3 (33.3)	—	1/5 (20)	—
<i>Dose (mg/day)</i>				
400 once daily	0/1 (0)	—	0/1 (0)	—
200 once daily	1/1 (100)	—	1/1 (100)	—
Definitive ribociclib interruption	1/3 (33.3)	—	2/5 (40)	—
Other	0/3 (0)	—	0/5 (0)	—