RESEARCH ARTICLE

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Real-World Effectiveness and Safety of Ribociclib Plus Aromatase Inhibitors in Patients with HR+/HER2- Metastatic Breast Cancer: A Multicenter Experience from Vietnam

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Abstract

Background: Although CDK4/6 inhibitors have demonstrated efficacy globally, real-world data from Vietnam are limited, primarily due to financial constraints. This study aimed to evaluate the effectiveness and toxicity of ribociclib combined with aromatase inhibitors (AIs) in patients with hormone receptor-positive, *HER2*-negative metastatic breast cancer (mBC) in a real-world study setting. **Methods:** This retrospective study included patients with de novo or recurrent hormone receptor-positive, *HER2*-negative metastatic breast cancer who were treated at two cancer centers between May 2021 and April 2024. The primary endpoint was progression-free survival (PFS), which was analyzed via the Kaplan–Meier method, with comparisons via the log-rank test and Cox regression. The secondary endpoints were the objective response rate (ORR) per RECIST 1.1, overall survival (OS), and adverse events graded by CTCAE 5.0. **Results:** A total of 92 female patients were eligible for the study. The mean age was 53.8±12.1 years. Among the patients, 69.6% received first line of treatment, and 30.4% were in subsequent lines. The median PFS (mPFS) was 19.1 months (95% CI: 14.3–26.2) in all patients, with a median follow-up time of 28.2 months. The rates of complete response, partial response, stable disease, and progressive disease were 2.2%, 55.4%, 37.0%, and 5.4%, respectively. PFS was lower in patients with liver metastasis (11.7 months vs. 21.8 months, p=0.030). With a median follow-up time of 27.9 months, the median OS was not reached, and the 3-year OS rate was 61.4%. Common adverse events (any grade/grade ≥3) included neutropenia (80.4/47.8%), elevated alanine transaminase (33.7%/3.3%), elevated aspartate transaminase (31.5%/3.3%), nausea (18.5%/0%), and thrombocytopenia (13.0%/0%). No treatment-related deaths were observed. **Conclusion:** Ribociclib combined with aromatase inhibitors demonstrated favorable real-world effectiveness and manageable safety profiles in Vietnamese patients with hormone receptor-positive, *HER2*-negative metastatic breast cancer in a real-world setting.

Keywords: Ribociclib- Aromatase inhibitors- Hormone receptor-positive breast cancer- *HER2*-negative metastatic

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Introduction

Breast cancer (BC) is the most common cancer among women and the second leading cause of cancer-related mortality worldwide, with nearly 666,103 deaths reported annually [1]. According to GLOBOCAN 2022, an estimated 2,295,686 new breast cancer cases are diagnosed in both sexes, with an age-standardized incidence rate of 46.8 per 100,000 women. In Vietnam, breast cancer is the most common cancer among women, with an increasing number of new cases, and ranks fourth in terms of cancer-related mortality. The age-standardized incidence rate is 38.0 per 100,000 women [2].

Approximately 5% of breast cancer patients are diagnosed with de novo metastasis, and approximately 30% of patients with localized breast cancer relapse within 5 years of initial diagnosis [3]. With adequate treatment, the median overall survival (OS) for patients with metastatic breast cancer (MBC) is 18–24 months, while the 5-year survival rate remains low at 5–20% [4]. In recent years, the median OS for MBC patients has increased due to significant advancements in diagnostics and treatment [5].

Hormone receptor-positive (HR+) and human epidermal growth factor receptor 2-negative (*HER2*-) breast cancer represents approximately 73% of all breast cancer cases [6]. Endocrine therapy has traditionally been the standard of care for HR+/*HER2*- metastatic breast cancer, demonstrating proven efficacy and favorable toxicity compared with chemotherapy [7]. CDK4/6

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inhibitors, such as ribociclib, have further improved progression-free survival (PFS) and OS rates and have good tolerability when combined with endocrine therapy. The MONALEESA-2, MONALEESA-3, and MONALEESA-7 trials revealed the role of ribociclib in combination with aromatase inhibitors (AIs) or fulvestrant, which resulted in increased OS and better disease control than did endocrine therapy alone [8-10]. In MONALEESA-2, ribociclib plus letrozole improved the median OS (63.9 vs 51.4 months), whereas MONALEESA-7 yielded similar results in premenopausal patients. Additionally, the CompLEEment-1 trial further validated the benefits and safety of ribociclib in broader patient populations [11].

In Vietnam, ribociclib combined with AIs has been approved as a first-line treatment option for patients with HR+/*HER2*- metastatic breast cancer since May 2021. However, access to this regimen as first-line therapy remains limited due to financial constraints, which may result in treatment outcome differences compared with global clinical trial findings. While CDK4/6 inhibitors have demonstrated proven efficacy in international studies, real-world data on their use in the Vietnamese population remain scarce. This study therefore aims to evaluate the real-world efficacy and safety profile of ribociclib combined with AIs in Vietnamese patients with recurrent or metastatic HR+/*HER2*- breast cancer, providing insights into treatment outcomes in a resource-limited healthcare setting.

Materials and Methods

Study population

This retrospective observational study included 92 female patients diagnosed with hormone receptor-positive, *HER2*/neu-negative advanced breast cancer (metastatic or recurrent) who were treated with ribociclib plus AIs at Vietnam National Cancer Hospital and Hanoi Oncology Hospital between May 2021 and April 2024.

Eligible participants were female patients aged 18 years or older with histopathologically confirmed breast carcinoma. Patients had either de novo metastatic (stage IV) or recurrent/metastatic disease confirmed by imaging, cytology, or histopathology and were not eligible for curative treatment. The tumors were hormone receptor-positive (ER and/or PR) and *HER2*-negative, as confirmed in both primary and metastatic lesions. Endocrine resistance was defined according to the Advanced Breast Cancer 3 (ABC3) consensus criteria. Recurrence occurring within 12 months after the completion of adjuvant endocrine therapy was considered endocrine-resistant, while recurrence beyond 12 months was classified as endocrine-sensitive. All patients had received at least two cycles of ribociclib in combination with an aromatase inhibitor for advanced disease. Additional inclusion criteria included an ECOG performance status of 0 to 3, adequate organ function (ANC $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, and bilirubin $\leq 1.5\times$ upper limit of normal), and complete medical records confirming the diagnosis, treatment history, and relevant clinical data.

Patients were excluded if they had previously received CDK4/6 inhibitors (including ribociclib) or AIs for advanced disease. Other exclusion criteria included progressive brain metastases with uncontrolled symptoms, a second active malignancy (except stable thyroid cancer, localized cervical cancer, or nonmelanoma skin cancer), and severe or uncontrolled chronic conditions that limited life expectancy. Pregnant or breastfeeding women, those with serious infections requiring ongoing treatment, and patients who declined participation were also excluded.

Treatment outcomes

The clinical and paraclinical data collected included age, disease stage, disease-free interval, menstrual status, metastatic site characteristics, histopathological type, endocrine receptor status, and treatment line. The disease-free interval was categorized as endocrine-sensitive (recurrence >12 months after adjuvant therapy) or endocrine-resistant (recurrence ≤12 months). Tumor response, including complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), was evaluated via the RECIST version 1.1 criteria. Clinical benefit (CB) was defined as CR, PR, or SD. PFS was measured from treatment initiation to disease progression or death from any cause. OS was defined as the time from the initiation of treatment to death from any cause. Toxicities were graded via CTCAE version 5.0.

Eligible patients were treated with 600 mg/day ribociclib for three consecutive weeks, followed by one week off, in combination with aromatase inhibitors (anastrozole 1 mg/day, letrozole 2.5 mg/day, or exemestane 25 mg/day) for 4-week cycles. Premenopausal patients additionally received goserelin 3.6 mg every 28 days.

Clinical examinations were conducted every two weeks during the first two treatment cycles and then at the end of each cycle. Treatment response was assessed every 2–3 cycles or sooner if disease progression was suspected. Toxicities were managed according to standard prescribing guidelines. Disease progression and mortality events were recorded throughout the study.

Data analyses

The data were analyzed via R software for Windows version 4.3.3 (https://cran.r-project.org/bin/windows/base/). Continuous data are presented as the means ± standard deviations or medians (interquartile ranges), and categorical data are presented as numbers (percentages). Comparisons were performed via Fisher's exact test and chi-square tests, as appropriate. PFS and OS were estimated via the Kaplan–Meier method and compared via the log-rank test. Multivariate Cox proportional hazard regression models with a backward elimination approach were utilized to evaluate factors associated with PFS. The median follow-up time was calculated via the reverse Kaplan–Meier method. A p value of < 0.05 was considered statistically significant.

Results

Patient characteristics

The patient characteristics are described in detail in Table 1. The mean age was 53.8 years (±12.1), with 66.3%

Table 1. Demographic and Clinical Characteristics of Patients

Characteristics	Number of Patients (n=92)	%
Age		
Mean Age (±SD)	53.8 ± 12.1	
< 60 years	61	66.3
≥ 60 years	31	33.7
Disease-free interval		
Recurrence >12 months after end of adjuvant therapy (Endocrine-sensitive)	16	17.4
Recurrence ≤12 months after end of adjuvant therapy (Endocrine-resistant)	30	32.6
De novo disease	46	50
Prior chemotherapy		
Yes	10	10.9
No	82	89.1
Menopausal Status		
Postmenopausal	62	67.4
Premenopausal	30	32.6
Metastatic Sites		
Bone	48	52.2
Local/regional	18	19.6
Lung	34	37
Liver	23	25
Brain	5	5.4
Lymph nodes	2	2.2
Others**	14	15.3
Number of Metastatic Sites		
1 site	43	46.7
2 sites	34	37
> 2 sites	15	15.3
Visceral Metastasis		
Present	50	54.3
Absent	42	45.7
Histopathological Type		
Invasive carcinoma of no special type (NST)	76	82.6
Invasive lobular carcinoma	6	6.5
Others***	10	10.9
Hormone Receptor Status		
ER-positive	91	98.9
PR-positive	77	83.7
Line of Therapy		
First-line	64	69.6
Second-line	21	22.8
Third-line	7	7.6
Distribution of aromatase inhibitors		
Letrozole	46	50
Anastrozole	38	41.3
Exemestane	8	8.7

*, Metastatic breast cancer at initial diagnosis; **, Includes pleura, pericardium, adrenal glands, and bone marrow; ***, Includes pleomorphic carcinoma, mixed ductal-lobular carcinoma, and micropapillary carcinoma

being under 60 years old. Most patients (67.4%) were postmenopausal. With respect to the disease-free interval, 50% had de novo disease, 32.6% had endocrine-resistant disease, and 17.4% had endocrine-sensitive disease. Among the recurrent cases, 30/46 patients (65.2%) underwent re-biopsy for pathological or molecular confirmation. Bone was the most common metastatic site (52.2%), followed by the lung (37.0%) and liver (25.0%). While nearly half of the patients (46.7%) had a single metastatic site, a substantial proportion (37%) had two sites, and 15.3% had more than two sites. Visceral metastasis was present in 54.3% of the patients. In terms of histopathology, invasive carcinoma of no special type (NST) was predominant (82.6%). This study included hormone receptor-positive patients, 98.9% of whom were ER positive and 83.7% of whom were PR positive. The majority of patients (69.6%) were receiving first-line therapy. The aromatase inhibitors were used in the following proportions: letrozole (50.0%), anastrozole (41.3%), and exemestane (8.7%).

As shown in Table 2, only 1 patient (1.1%) discontinued treatment because of toxicity. The majority of patients (67.4%) maintained the initial dose of ribociclib, whereas 27.2% and 4.3% needed level 1 and 2 dose reductions, respectively. Nearly half of the patients (48.9%) experienced at least one delay, whereas 51.1% had no interruptions.

Objective response

The overall ORR was 57.6% in all patients, with 2.2% achieving a CR and 55.4% achieving a PR. Among patients with measurable disease (N = 80), the ORR increased to 63.8%, including 2.5% with a CR and 61.3% with a PR (Table 3).

Table 2. Ribociclib Dosage and Treatment Features

Characteristics (%)	Number of Patients (n)	Percentage (%)
Dose Reduction		
Maintained initial dose	62	67.4
Dose reduction level 1	25	27.2
Dose reduction level 2	4	4.3
Discontinued due to toxicity	1	1.1
Treatment Delay		
No delay	47	51.1
Delay occurred	45	48.9

Table 3. Objective Response Rates in All Patients and in Those with Measurable Disease

Treatment Response	All Patients N = 92 (%)	Patients with Measurable DiseaseN = 80 (%)
Complete response (CR)	2 (2.2)	2 (2.5)
Partial response (PR)	51 (55.4)	49 (61.3)
Stable disease (SD)	34 (37.0)	24 (30.0)
Progressive disease (PD)	5 (5.4)	5 (6.3)
Overall response rate (ORR)	53 (57.6)	51 (63.8)
Disease control rate (DCR)	87 (94.6)	75 (93.8)

Table 4. Progression-Free Survival and Related Factors

Factors	mPFS	Univariate analysis (*)		Multivariate analysis (**)	
		p	HR (95% CI)	p	HR (95% CI)
Age					
< 60 years	19.1	0.234	1.00 (reference)	-	-
≥ 60 years	19.0		1.40 (0.80-2.46)		
Line of Treatment					
First-line	20.7	0.702	1.00 (reference)	-	-
Second-line and beyond	17.1		1.12 (0.63-1.99)		
Prior Endocrine Therapy					
No prior endocrine therapy or Endocrine-sensitive	21.3	0.815	1.00 (reference)	-	-
Endocrine-resistant	16.1		1.07 (0.60-1.90)		
Menopausal Status					
Premenopausal	21.4	0.111	1.00 (reference)	-	-
Postmenopausal	18.2		1.66 (0.88-3.12)		
Liver Metastasis					
No	21.8	0.030	1.00 (reference)	0.069	1.00 (reference)
Yes	11.7		1.92 (1.05-3.51)		1.73 (0.96-3.11)
PR expression					
Negative	18.2	0.159	1.00 (reference)	-	-
Positive	21.8		0.62 (0.31-1.22)		
Number of Metastatic Sites					
1 site	17.5	0.534	1.00 (reference)	-	-
≥ 2 sites	16.1		0.85 (0.55-1.31)		
Visceral metastases					
No	22.9	0.078	1.00 (reference)	-	-
Yes	16.1		1.64 (0.94-2.88)		
Dose Reduction					
No reduction	19.0	0.056	1.00 (reference)	0.082	1.00 (reference)
Dose reduction	NR		0.52 (0.27-1.03)		0.56 (0.29-1.08)

HR, Hazard ratio; CI, Confidence Interval; mPFS, median progression-free survival; (*), Log-rank test; (**), Cox regression multivariate analysis

Progression-free survival

The median follow-up time was 28.2 months (95% CI 19.5-31.7 months) from the start of ribociclib treatment. At the time of analysis in May 2025, 52 (56.5%) patients experienced progression. The median PFS was 19.1 months (95% CI 14.3-26.2 months) in all patients (Figure 1).

Table 4 presents the median PFS and related factors. The data indicate that age has no impact on PFS, with patients under 60 years having a similar PFS (19.1 months) to those over 60 years (19.0 months). The median PFS was 21.4 months in premenopausal patients and 18.2 months in postmenopausal patients; however, this difference was not statistically significant (p = 0.111). PFS was similar between treatment lines: 20.7 months for first-line therapy and 17.1 months for second-line therapy or later (p = 0.702). PFS also did not differ significantly between endocrine-resistant patients and those with de novo stage IV or endocrine-sensitive disease (16.1 vs. 22.9 months; p = 0.815). Patients with liver metastases had significantly worse PFS (11.7 months) than did those without liver metastases (21.8 months, p=0.030). The number of metastatic sites did not markedly affect PFS (p=0.534). Median PFS was longer in patients without visceral metastases than in those with visceral involvement (22.9 vs. 16.1 months), though the difference did not reach statistical significance (p = 0.078). Patients with positive PR expression had a longer median PFS than did those with negative PR expression (21.8 vs. 18.2 months), although the difference was not statistically significant (p = 0.159). Notably, patients who required dose reduction appeared to have a numerically longer PFS (not reaching the median PFS vs. 19.0 months), although this difference was not statistically significant (p = 0.056).

In the multivariable analysis with backward stepwise selection, liver metastasis and dose reductions remained in the final model. Liver metastasis was associated with a clinically relevant but statistically non-significant increase in the risk of progression (HR = 1.73, 95% CI 0.96–3.11; p = 0.069). Conversely, patients who required dose reductions had a non-significant 44% lower risk of progression (HR = 0.56, 95% CI 0.29–1.08; p = 0.082) (Table 4).

Overall survival

With a median follow-up time of 27.9 months (95%

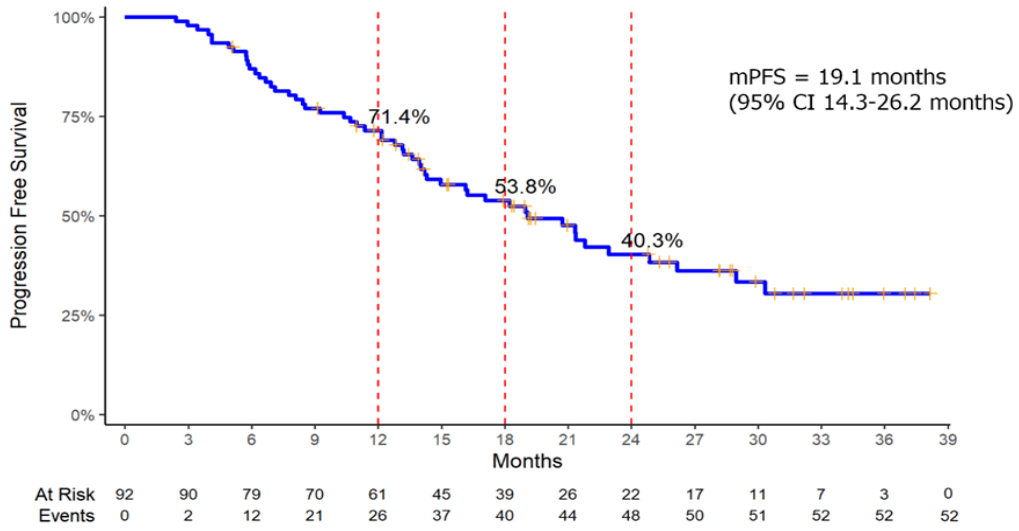

Figure 1. Kaplan–Meier Curve of the Progression-Free Survival of the Study Population

CI, 22.9-30.6 months), the median OS was not reached, with 28.3% of events having occurred. The 1-year, 2-year, and 3-year OS rates were 88.0%, 69.2%, and 61.4%, respectively (Figure 2).

Adverse events

Table 5 summarizes the most common treatment-related adverse events observed in the study population, including hematologic and non-hematologic toxicities. Neutropenia was the most frequently reported severe adverse event, with 40.2% of patients experiencing Grade 3 adverse events and 7.6% experiencing Grade 4 adverse events. Thrombocytopenia and anemia were mostly mild, with only 1.1% and 3.3% of patients experiencing Grade 2 toxicity, respectively. Non-hematologic toxicities were generally mild, with fatigue, hot flashes, nausea, and vomiting being the most frequently reported symptoms, predominantly grade 1. Gastrointestinal toxicity (diarrhea) and dermatitis are rare, with most patients experiencing no symptoms. Elevated liver enzymes (AST and ALT) were observed in a small proportion of patients, with a few patients reaching Grade 3 or 4 severity. Notably, no patients experienced QT prolongation on ECG. The overall safety profile suggests that hematologic toxicity, particularly neutropenia, is a significant adverse event and that other side effects are mild and manageable.

Discussion

Ribociclib combined with AIs showed efficacy and safety in the MONALEESA-2 and MONALEESA-7 phase III trials as a first-line treatment for advanced HR+/*HER2*- breast cancer. It was approved for use in Vietnam in May 2021. However, high costs and limited insurance coverage restrict access for many patients. This study examined outcomes in 92 patients with recurrent or metastatic HR+/*HER2*- breast cancer treated with this regimen at K Hospital and Hanoi Oncology Hospital between May 2021 and April 2024.

Our cohort included patients with recurrent or metastatic HR+/*HER2*- breast cancer treated with ribociclib plus AIs as either first-line or later-line

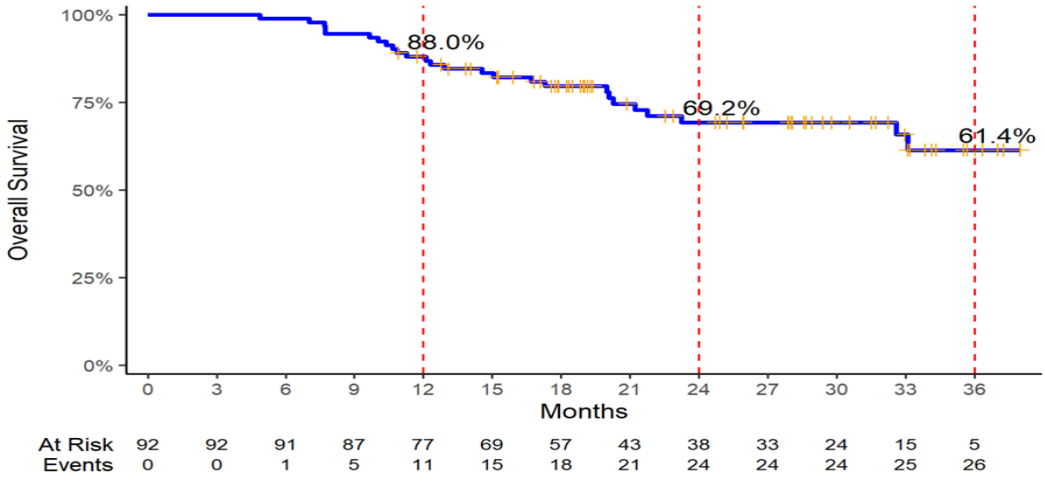

Figure 2. Kaplan–Meier Curve of the Overall Survival of the Study Population

Table 5. Most Common Treatment-Related Adverse Events

Adverse Events	Patients, n=92 (100%)				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia	18 (19.6)	9 (9.8)	21 (22.8)	37 (40.2)	7(7.6)
Thrombocytopenia	80 (87.0)	11 (12.0)	1 (1.1)	0	0
Anemia	68 (75.6)	19 (21.1)	3 (3.3)	0	0
Fatigue	90 (97.8)	2 (2.2)	0	0	0
Hot flashes	61 (66.3)	31 (33.7)	0	0	0
Nausea	75 (81.5)	17 (18.5)	0	0	0
Vomiting	83 (90.2)	9 (9.8)	0	0	0
Musculoskeletal pain	72 (78.3)	20 (21.7)	0	0	0
Diarrhea	91 (98.9)	1 (1.1)	0	0	0
Dermatitis	90 (97.8)	2 (2.2)	0	0	0
Elevated AST (Aspartate Aminotransferase)	63 (68.5)	18 (19.6)	8 (8.7)	2 (2.2)	1 (1.1)
Elevated ALT (Alanine Aminotransferase)	61 (66.3)	20 (21.7)	8 (8.7)	1 (1.1)	2 (2.2)
QT prolongation on ECG	92 (100)	0	0	0	0

therapy. Most patients (69.6%) received the combination in the first-line setting. Ten patients (10.9%) had prior chemotherapy for advanced disease, unlike participants in the MONALEESA-2 and MONALEESA-7 trials, who were treatment-naïve for advanced disease. These patients who received prior chemotherapy did so because CDK4/6 inhibitors were not available at the time of metastatic disease diagnosis or because chemotherapy was chosen at the treating physician's discretion. Similarly, in the CompLEEment-1 study, 10% (n=324) had received chemotherapy for advanced disease. Regarding AI selection, the study included anastrozole and exemestane (used in 41.3% and 8.7% of cases, respectively) in addition to letrozole, based on regulatory guidance and clinical practicality. Local drug availability in real-world context also played a role in AI selection.In our cohort, 32.6% (n=30) of the patients exhibited endocrine resistance which was higher than that reported in MONALEESA-2, MONALEESA-7, and CompLEEment-1. This higher rate of endocrine resistance can be attributed to clinical practice patterns in Vietnam, where many patients with hormone receptor-positive breast cancer are still treated with the adjuvant tamoxifen. Consequently, a substantial proportion of patients who develop endocrine-resistant recurrence are subsequently treated with AIs plus ribociclib for advanced disease.

Progression-free survival is a crucial endpoint for evaluating the efficacy of a drug in treating recurrent or metastatic cancer. With a median follow-up time of 28.2 months, the median PFS in our cohort was 19.1 months (95% CI: 14.3 to 26.2 months), with 56.5% of patients experiencing disease progression. The PFS rates at 12, 18, and 24 months were 71.4%, 53.8%, and 40.3%, respectively. Our findings revealed a lower median PFS than the MONALEESA-7 trial (23.8 months) [10] and the MONALEESA-2 trial (25.3 months) [12]. Our findings align with those of the BrasiLEEria study, which reported a 1-year PFS rate of 77.6% in patients with HR-positive, *HER2*-negative metastatic breast cancer receiving first-line ribociclib plus Ais [13]. Similarly, an Australian study of 160 patients with the same disease and treatment reported PFS rates of 76% at 12 months, 67% at 18 months, and 64% at 24 months slightly higher than those reported in our cohort [14]. A real-world study in Vietnam assessed the effectiveness of first-line palbociclib or ribociclib combined with either an aromatase inhibitor or fulvestrant in patients with hormone receptor–positive metastatic breast cancer. PFS rates at 6, 12, and 18 months were 94.4%, 93.5%, and 91.5%, respectively [15]. In another real-world study from a resource-limited country, 350 patients with metastatic breast cancer received ribociclib plus either an aromatase inhibitor or fulvestrant. After a median follow-up of 36.3 months, the median PFS was 27.3 months (95% CI: 21.3–31.7). PFS was significantly longer among patients treated with ribociclib as first-line therapy (32.1 months; 95% CI: 27.7–42.1; $p < 0.0001$) and those with non-visceral metastases (38.6 months; 95% CI: 29.8–NR; $p < 0.0001$) [16]. This difference may be explained by the fact that those trials primarily included patients receiving first-line therapy, as well as potential differences in patient populations, treatment settings, and tumor biology.

Among the factors associated with PFS, patients with liver metastases had significantly shorter survival (11.7 vs. 21.8 months, $p = 0.030$), echoing earlier studies identifying liver metastases as poor prognostic factors. Visceral metastases, especially liver involvement, indicate a poor prognosis in patients with breast cancer due to aggressive disease and a limited response to endocrine therapy [17, 18]. CDK4/6 inhibitors offer substantial benefit in this subgroup. A pooled analysis of the MONALEESA trials revealed that ribociclib reduced the risk of death by 19% among patients with visceral metastases (HR 0.81) and 29% among patients with liver cancer (HR=0.71) [19]. Despite treatment with ribociclib, in this pooled analysis, patients with liver metastases had numerically shorter OS than those with visceral metastases overall: 39.6 months versus 49.0 months [19].

Compared with patients with de novo stage IV or endocrine-sensitive disease, patients with endocrine-

resistant disease showed a non-significant trend toward shorter PFS (19.0 vs. 22.9 months, p = 0.815). Endocrine resistance is defined as recurrence within 12 months of completing adjuvant endocrine therapy or progression within 6 months of first-line endocrine therapy for metastatic disease [20]. These tumors are less responsive to hormonal suppression and carry a poorer prognosis. Historically, chemotherapy has been the preferred treatment [21]. However, CDK4/6 inhibitors still improve PFS when combined with endocrine therapy in patients with endocrine-resistant disease, as shown in trials such as MONALEESA-3 and MONARCH 3 [8, 22].

PFS did not vary significantly by prior therapy line, age, histological subtype, or number of metastatic sites. We observed no significant difference in PFS between patients treated with ribociclib plus AIs in the first-line setting and those treated in the subsequent-line setting (20.7 vs. 17.1 months, p=0.702). These findings are consistent with those reported by Fountzilas et al., who reported median PFSs of 18.7, 12.0, and 7.4 months for first-, second-, and third-line treatments, respectively, in a cohort of 365 patients receiving CDK4/6 inhibitors and endocrine therapy. However, their study demonstrated a clear trend toward decreased efficacy with later lines of treatment, which was not evident in our cohort when first-line versus subsequent-line therapy was compared [23]. Additionally, the SONIA trial similarly reported no difference in outcomes between patients receiving CDK4/6 inhibitors before and after prior endocrine therapy [24]. These collective findings suggest that ribociclib plus AI combination therapy may maintain its efficacy regardless of the treatment line, supporting the potential for flexible treatment sequencing in clinical practice.

Dose reductions or treatment delays did not significantly affect treatment efficacy in our study. In fact, patients who underwent dose reductions tended to have longer PFS than did those who did not (median PFS not reached [16.1, NR] vs. 19.0 months [13.1, 26.2]; p = 0.056). Data analyzed from the MONALEESA-2, MONALEESA-3, and MONALEESA-7 trials provide important evidence supporting the maintenance of treatment efficacy despite dose reductions. Among patients who did not require ribociclib dose reductions, the median PFS compared with placebo was as follows: MONALEESA-2 (27.7 vs. 16.0 months), MONALEESA-3 (not reached vs. 18.3 months), and MONALEESA-7 (23.8 vs. 13.8 months). Notably, patients who had at least one dose reduction still maintained impressive median PFS outcomes: MONALEESA-2 (25.3 months), MONALEESA-3 (not reached), and MONALEESA-7 (27.5 months) [25]. Among those with measurable disease, objective response rates (ORRs) were numerically higher in patients who had dose reductions than in those who did not: MONALEESA-2 (62% vs. 46%), MONALEESA-3 (57% vs. 43%), and MONALEESA-7 (55% vs. 48%) [25]. Real-world data from 319 premenopausal patients in the Turkish Oncology Group revealed similar trends: the median PFS was 32.0 months in the dose-reduction group and 25.96 months in the full-dose group (p = 0.238) [26].

Ribociclib plus endocrine therapy has shown strong clinical benefits and survival outcomes in patients with recurrent or metastatic breast cancer. The overall ORR in our study was 57.6% (Table 3), which is comparable to that reported in previous clinical trials, such as MONALEESA-2 (ORR 40.7%) [27] and MONALEESA-7 (51%) [28]. Notably, the clinical benefit rate (CBR) exceeded 94%, demonstrating a high rate of disease control, even in subgroups with multiple metastatic sites or those receiving second-line or later therapy. A real-world study conducted in Vietnam evaluated the effectiveness of CDK4/6 inhibitors (ribociclib or palbociclib) combined with either aromatase inhibitors or fulvestrant in 108 patients with HR-positive, *HER2*-negative metastatic breast cancer. The reported ORR and CBR were 28.8% and 70.3%, respectively, reflecting potential variations in treatment outcomes [15].

Common adverse events (AEs) in our cohort included neutropenia, elevated liver enzymes, hot flashes, nausea and vomiting, fatigue, and arthralgia. No new safety signals emerged. Neutropenia occurred most frequently (80.4% any grade; 47.8% grade ≥3), which is consistent with previous reports. Despite the high rate of grade 3/4 neutropenia, no cases of febrile neutropenia were observed. For grade 3–4 neutropenia, treatment was delayed and patients were closely monitored until recovery to grade 2. Dose reduction was implemented according to the guidelines in cases of grade 4 neutropenia, recurrent grade 3 neutropenia, or grade 3 neutropenia accompanied by fever.In comparison, the MONALEESA-2 trial reported any-grade neutropenia in 77.2% of patients, including 53.3% grade 3 and 9.9% grade 4 events. Elevated liver enzymes (ALT, AST) and thrombocytopenia were also common, mostly Grade 1–2. Liver enzyme elevation occurred in ~30% of patients, with Grade ≥3 rates of approximately 3–5%, similar to the MONALEESA-7 data (AST 5%, ALT 5%). For grade 3 hepatotoxicity (elevated liver enzymes), treatment was withheld until liver function returned to baseline grade, after which a dose reduction was implemented. Ribociclib was permanently discontinued in cases of grade 4 hepatotoxicity or recurrent grade 3 elevation. In a real-world study conducted in Italy involving 78 patients with metastatic breast cancer treated with ribociclib in combination with endocrine therapy, 21.8% of patients had liver metastases. The overall incidence of transaminase elevation was 8.8% (7 patients) across the study population [29], which was lower than that reported in our study. The higher rate of hepatotoxicity in our cohort may reflect the greater proportion of patients with liver metastases (25%) and the use of ribociclib in later treatment lines. Prior therapies could impair liver function, increasing susceptibility to toxicity. Other AEs such as anemia, nausea, vomiting, musculoskeletal pain, stomatitis, diarrhea, and alopecia were mostly mild (Grade 1). A known adverse effect specific to ribociclib is QT interval prolongation on an electrocardiogram (ECG). Approximately 2.8% of patients experience QTc prolongation beyond 480 ms during ribociclib treatment[30], highlighting the importance of ECG monitoring before and during treatment particularly within the first two weeks of each cycle for early detection.

In our study, ECGs were routinely conducted at baseline, mid-cycle 1, and at the beginning of cycle 2, then as clinically indicated thereafter, in accordance with standard practice and product labeling. However, in our study, no QTc prolongation was observed. Although toxicity rates may seem higher than those reported in some studies, this likely reflects our method of recording the maximum grade per patient and the modest sample size. Overall, the toxicities were manageable, with no treatment-related deaths and only one discontinuation due to grade 4 liver enzyme elevation (1.1%), indicating good tolerability in real-world settings.

This study has several limitations due to its retrospective, observational design. First, the absence of a control group prevents firm conclusions about the efficacy of ribociclib plus aromatase inhibitors. Second, selection bias may have influenced the results, as patients with better performance status and access to treatment were likely overrepresented. Third, although the sample size (n=92) offers valuable real-world insights, it remains small and may not reflect the full spectrum of treatment responses. The inclusion of patients previously treated with chemotherapy for advanced disease (10.9%) and a higher rate of endocrine resistance (32.6%) than those in major trials may also explain the shorter median PFS. Differences in follow-up, monitoring, and treatment settings further limit comparability with randomized trials. Finally, unmeasured factors such as tumor biology, adherence, and socioeconomic status may have confounded the outcomes. Nevertheless, this study provides meaningful real-world evidence on the safety and effectiveness of ribociclib plus AIs in Vietnamese patients with advanced HR+/*HER2*− breast cancer.

In conclusion, this real-world study provides important evidence supporting the effectiveness and manageable safety profile of ribociclib combined with AIs in Vietnamese patients with hormone receptor-positive, *HER2*-negative metastatic breast cancer. The observed median PFS of 19.1 months and 3-year OS rate of 61.4% are comparable with global clinical trial data. Liver metastasis was associated with significantly shorter PFS, highlighting the need for tailored strategies in high-risk subgroups. The treatment was generally well tolerated, with neutropenia being the most common adverse event, but no treatment-related deaths were reported. These results support the role of CDK4/6 inhibitors in routine clinical practice and underscore the importance of improving access to advanced therapies in low- and middle-income countries.

Author Contribution Statement

Hoa Thi Nguyen: Conceptualization, Methodology, Formal analysis, Writing - Original Draft, Writing - Review & Editing, Project administration. Quang Van Le: Conceptualization, Methodology, Writing - Original Draft, Writing - Review & Editing, Supervision. Huyen Thi Phung: Methodology, Investigation, Resources, Writing - Review & Editing. Quang Hong Nguyen: Investigation, Resources. Huong Thi Minh Vu: Investigation, Resources. Minh Cong Truong: Software, Formal analysis, Visualization, Writing - Review & Editing.

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Scientific Approval/Student Thesis

This study is part of a PhD thesis and was approved by the Biomedical Research Ethics Committee of Hanoi Medical University (approval number No. 918/GCN-HDDDNCYSH-DHYHN, dated June 30, 2023).

Data Availability

The de-linked and anonymized datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Declaration

The Biomedical Research Ethics Committee of Hanoi Medical University in Hanoi, Vietnam approved this study and waived the informed consent for the study due to its retrospective nature and the absence of patient safety concerns. In addition, patient records were anonymized and de-identified before undergoing analysis.

Conflict of Interest

The Authors declare that there is no conflict of interest

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