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ORIGINAL RESEARCH

Clinical Outcomes of Patients Treated with Ribociclib in Combination with Aromatase Inhibitors or Fulvestrant for HR-Positive, HER2-Negative Metastatic Breast Cancer, Real-World Data from a Low-Resourced Country

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Background: Cyclin-dependent kinase (CDK) 4/6 inhibitors have revolutionized the treatment landscape of hormone receptor-positive (HR+) and human epidermal growth factor receptor 2-negative (HER2 −) metastatic breast cancer (MBC). Here, we present the real-world clinical outcomes and toxicity data of patients treated at a single cancer center.

Methods: A retrospective analysis was conducted on patients with HR+/HER2− MBC treated with ribociclib plus endocrine therapy (ET). Outcomes measured included progression-free survival (PFS), overall survival (OS), and adverse events.

Results: A total of 356 patients (median age 52, range 27–91 years) were enrolled, all with metastatic disease; 204 (57.5%) had de novo metastasis, and 183 (51.4%) had visceral metastasis. Ribociclib was combined with aromatase inhibitors in 321 patients (90.2%) and with fulvestrant in 35 patients (9.8%). Dose reduction was needed in 101 patients (28.4%), primarily due to neutropenia (21.3%) and abnormal liver enzymes (5.9%). After a median follow-up of 36.3 months, median PFS was 27.3 months (95% CI: 21.3–31.7). PFS was significantly better in patients receiving ribociclib as first-line therapy (32.1 months, 95% CI: 27.7–42.1, $p < 0.0001$) and those with non-visceral metastasis (38.6 months, 95% CI: 29.8–NR, $p < 0.0001$). Similarly, OS was significantly better in first-line treatment (48.6 months, 95% CI: 39.1–NR) and non-visceral metastasis cases (NR, 95% CI: 40.6–NR, $p < 0.0001$). No significant differences in 3-year PFS and OS were found between patients with and without dose reductions.

Conclusion: In real-world settings, and away from the stringency of controlled clinical trials, endocrine therapy in combination with ribociclib in patients with HR-positive/HER2-negative MBC is an effective and well-tolerated therapy with a manageable toxicity profile and a low drug discontinuation rate. Dose reduction due to toxicity did not worsen the outcome.

Keywords: metastatic breast cancer, MBC, CDK4/6 inhibitors, ribociclib, aromatase inhibitors, fulvestrant

Introduction

Breast cancer continues to be the most frequently diagnosed cancer worldwide and also a leading cause of cancer-related mortality.[1] Though the proportion of patients who present with locally advanced or metastatic disease is shrinking in Western societies, it is still a problem in low-resourced countries, like ours.[2–4] Additionally, a proportion of patients who present with early-stage disease may progress despite anti-cancer therapy.

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Breast cancer expressing the estrogen receptor (ER) and/or progesterone receptor (PR), known as hormone receptor-positive (HR+) and human epidermal growth factor receptor 2–negative (HER2-) breast cancer, is the most common subtype, accounting for over 70% of all breast cancers.[5]

Endocrine therapy (ET) has consistently been the cornerstone of treatment for HR+/HER2- breast cancer.[6] However, acquired drug resistance is frequently encountered.[7,8] Over the last decade, several new approaches have been introduced in clinical practice to tackle many of the recently identified pathways that mediate such resistance.[9,10] Cyclin-dependent kinases (CDK) are protein kinases that bind to cyclin D1, resulting in the formation of an activated complex, which then phosphorylates and inactivates the tumor suppressor retinoblastoma protein to release E2F transcription factors, resulting in cell cycle progression and cancer cell proliferation. This pathway can be competitively inhibited using a highly selective CDK4/6 inhibitors.[11,12] CDK4/6 inhibitors have revolutionized the treatment landscape HR+, HER2- metastatic breast cancer with significant improvement in progression-free survival (PFS) and, in some of them, overall survival (OS), too.[13] PALOMA-2 was the first clinical trial to show an improvement in PFS of postmenopausal women treated, in the first-line setting, with a combination of palbociclib and endocrine treatment versus endocrine treatment alone.[14,15] Several other studies confirmed the improved PFS with the addition of CDK4/6 inhibitors, including ribociclib and abemaciclib, in several other clinical settings irrespective of the line of treatment (first-line, second-line and beyond), menopausal status (both premenopausal and postmenopausal), and the companion ET; aromatase inhibitors (AI) or fulvestrant.[16] More recently, the overall survival (OS) advantage was demonstrated numerically in all agents and statistically with ribociclib and abemaciclib.[17] The three CDK4/6 inhibitors have been approved by the US Food and Drug Administration (FDA) for the treatment of HR-positive/HER2-negative locally advanced or metastatic breast cancer (MBC).[14,18,19]

Real-world data is a useful tool that enables clinicians to better assess the clinical benefit and safety profile of new treatment regimens in subgroup of patients that are often excluded from clinical trials, such as minorities, non-Western, older patients, patients with multiple comorbidities and poor performance status.[20,21] Real-world data can also be used by regulatory agents to ensure that clinical outcome data are reproducible in daily clinical practice, and may occasionally modify the indications and administration patterns of such therapy.[22] Though some of the CDK4/6 inhibitors clinical trials attempted to address the concept of "diversity and inclusion", the proportion of such patients enrolled was not enough.

In this study, we retrospectively analyzed the demographic and clinical characteristics and treatment outcomes (both safety and outcome) of patients with HR+/HER2- MBC treated with endocrine therapy (AI or fulvestrant) combined with CDK4/6 inhibitors at the King Hussein Cancer Center, a standalone tertiary cancer center.

Methods

This study was a retrospective analysis of individual patient data. All consecutive patients with HR+/HER2- MBC who were treated and followed-up at our institution with ribociclib plus endocrine treatment between June 2017 and May 2020 were included. Data were collected from patients' electronic medical records.

All patients were adults aged ≥18 years with pathologically confirmed breast cancer. All pathological specimens were processed, read, or reviewed at our center. All pathological characteristics, including histological subtype (invasive ductal, invasive lobular, and others), tumor grade, and lymphovascular invasion were collected. Hormonal receptor status was determined by immunohistochemical staining, and patients were offered endocrine therapy if their ER and/or PR was ≥10%. Additionally, all patients were HER2-negative, as determined by immuno histochemistry (IHC) scores of zero or +1, while those with +2 score were mandated to have negative in situ hybridization (ISH) or fluorescence in situ hybridization (FISH). Metastatic diseases have been confirmed either by biopsy of the metastatic site or by imaging, when consistent findings are observed on two different modalities, such as computed tomography scan and bone scan. Visceral metastasis was defined as the documented involvement of the lungs, liver, and/or central nervous system. Ribociclib was administered at a daily dose of 600 mg from day-1 to day-21 of the 28-day cycle, whereas aromatase inhibitors (letrozole (2.5 mg) or anastrozole (1 mg)) were administered daily. Fulvestrant, which was given to patients who have previously received aromatase inhibitors in either the adjuvant or metastatic setting, was administered intramuscularly at a dose of 500 mg as two 5 mL injections, one in each buttock, on days 1, 15, and 29, and once

monthly thereafter. In premenopausal women, ovarian ablation was mandated prior to starting AI, and was accomplished by luteinizing hormone-releasing hormone (LHRH) agonists or surgical oophorectomy in a few patients. Dose reduction, interruption, and discontinuation of ribociclib were performed as clinically indicated, according to guidelines based on adverse events. Patients were divided into two groups based on the timing of metastasis: those whose initial presentation was confirmed as metastatic disease (de novo MBC) and those who relapsed after initial treatment for early-stage disease (recurrent).

Statistical Analysis

Descriptive statistics were used to summarize patient characteristics. Continuously scaled measures are summarized by median and range values, while categorical data, including frequencies and percentages, are described in the tables. Baseline patient and disease-specific characteristics were compared using the chi-square test.

The primary endpoint was progression-free survival (PFS), defined as the time from treatment initiation with CDK4/6 inhibitors until the first documented disease progression, death from any cause, or the last follow-up, whichever occurred first. The secondary endpoint was overall survival (OS), defined as the time from treatment initiation with CDK4/6 inhibitors until the date of death from any cause or the last follow-up. Additional secondary endpoints included adverse events, dose reduction, and discontinuation rates. Survival outcomes were estimated using the Kaplan–Meier method, and survival comparisons were conducted using the Log rank test. Subgroup analysis was performed based on the line of therapy (first-line, second-line, third, or beyond), menopausal status, site of metastasis, and companion ET (AI or fulvestrant). Univariate analyses (using Log rank tests) and multivariate analyses (using the Cox proportional hazards model) were performed to assess the impact of known prognostic variables on PFS and OS, a p-value of <0.05 was considered statistically significant. SAS V.9.3 (SAS Institute) was used for analysis.

Owing to its retrospective nature and lack of patient identifiers, the study was exempted from full review by the Institutional Review Board (IRB) at King Hussein Cancer Center, and the requirement for informed consent was waived. The study was conducted in compliance with all local and international laws, including the guidelines outlined in the Declaration of Helsinki.

Results

Patients Characteristics

During the study period, 356 eligible patients were treated with ET and CDK4/6 inhibitors and were enrolled in this analysis. All patients had a confirmed diagnosis of MBC and were female. The median age was 52 (27–91) years, and 167 patients (46.9%) were premenopausal. The majority of the patients had good Eastern Cooperative Oncology Group (ECOG) performance status of zero (n=216, 62.1%) and 1 (n=116, 33.3%). The most common tumor histology was invasive ductal carcinoma (IDC) (n=285, 80.1%), and the majority of patients had high-grade disease (106 (32.0%)) grade-3 and 199 (60.1%) grade-2.

All enrolled patients had a confirmed diagnosis of metastatic breast, with more than half (n=204, 57.5%) presenting (de novo metastasis). The bone was the most common site of metastasis (n=154, 43.3%); however, bone-only metastasis was reported in 128 (36.0%) patients. Visceral metastasis at the time of treatment initiation involved the liver in 89 (25.0%), the lungs in 73 (20.5%) patients, and brain in 11 (3.1%) patients. All patients, according to the selection criteria, had HER-2 negative disease; however, 146 (441.1%) had HER2-low disease, as determined by IHC (Table-1).

Treatment: ET and Ribociclib

The majority (n=227, 63.8%) received CDK4/6 inhibitors as first-line therapy, while the others received them as second-line therapy (n=81, 22.8%) or beyond (n=48, 13.5%). Ribociclib was used in combination with AI in 321 patients (90.2%) and with fulvestrant in 35 patients (9.8%). Dose reduction was required in 101 patients (28.4%). The most common reasons for dose reduction were neutropenia (n=76, 21.3%) and abnormal liver enzyme level (n=21, 5.9%). A total of 28 (7.9%) patients discontinued treatment due to toxicities; both cardiac and liver toxicities (n=6, 21.4%) were the most common culprit. Renal toxicity caused discontinuation in 5 (17.9%) patients, while 3 (10.7%) discontinued the

Table 1 Patients' Characteristics (N=356)

Variable	Level	Frequency	Percentage
ECOG Performance Status	0	216	62.1
	1	116	33.3
	2	13	3.7
	3 /4	3	0.8
	Unknown	8	2.3
Menopausal Status	Postmenopausal	189	53.1
	Premenopausal	167	46.9
Smoking history	Current smoker	44	12.4
	Never smoked	270	75.8
	Unknown	24	6.7
	X-Smoker	18	5.1
Histology	IDC	285	80.1
	ILC	55	15.4
	Others	16	4.5
HER2 Status	0	194	57.1
	1	108	31.8
	2	38	11.2
	Unknown	16	4.5
Tumor grade	1	26	7.9
	2	199	60.1
	3	106	32.0
	Unknown	25	7.0
Timing of Metastasis	De novo	204	57.5
	Recurrent	151	42.5
Site of Metastasis	Bone	154	43.3
	Brain	11	3.1
	Liver	89	25.0
	Lung	73	20.5
	Others	15	4.2
Visceral vs non-visceral	Non-visceral	173	48.6
	Visceral	183	51.4

Abbreviations: ECOG, Eastern Cooperative Oncology Group.

drug because of pneumonitis. The remaining patients discontinued the drug during the COVID-19 pandemic period. However, no deaths occurred due to toxicity. Table-2 summarizes the treatment regimens and associated toxicities.

Treatment Outcomes

At the time of data analysis with a median follow-up of 36.3 (range, 0.0–78.1) months, and 211 censored events, the median OS for the whole group, irrespective of the line of therapy, was 40.6 months (95% CI, 33.5–48.6), while the median PFS was 27.3 months (95% CI, 21.3–31.7). The 12-month and 24-month OS rates were 90.5% (95% CI, 87.2–93.4) and 72.7% (95% CI, 67.8–77.4), respectively, while the 12-month and 24-month PFS were 73.1% (95% CI, 68.4–77.7) and 53.6% (95% CI, 48.3–58.9), respectively.

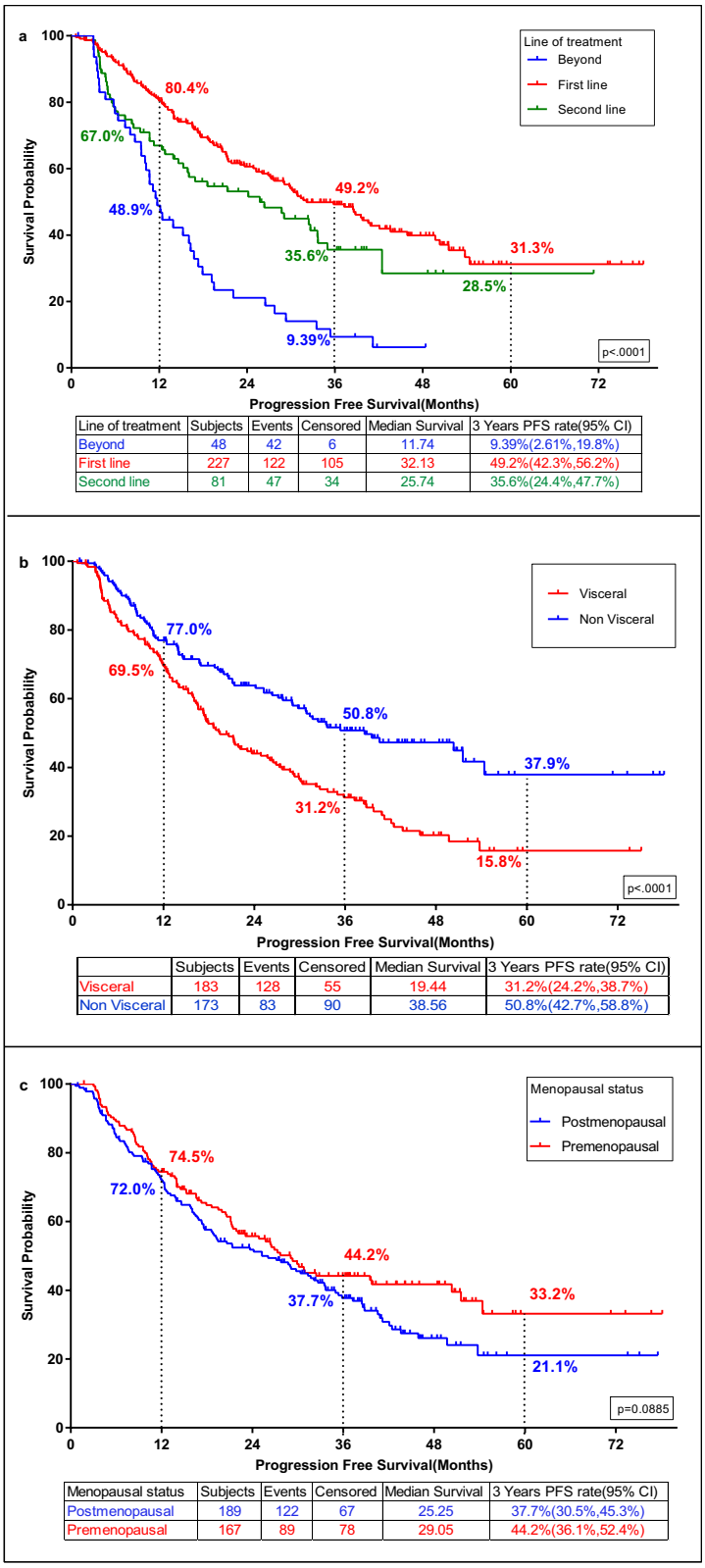
Median PFS for patients who received CDK4/6 inhibitors as first-line was better (32.1 months; 95% CI 27.7–42.1) compared to those who received as a second line (25.7 months, 95% CI 15.3–33.7) or beyond the second line (11.7 months, 95% CI 9.6–16.3), p<0.0001 (Figure 1a). Additionally, PFS was better for patients treated with CDk4/6 inhibitors for non-visceral metastasis (38.6 months, 95% CI 29.8-NR) than for those with visceral metastasis (19.4 months, 95% CI 16.6–26.1), p<0.0001, Figure 1b. However, PFS was not different in postmenopausal (25.3 months, 95% CI 18.6–32.7) versus premenopausal women (29.1 months, 95% CI 21.9–50.3), p=0.089, Figure 1c.

The median OS for the whole group, irrespective of menopausal status, line of therapy or site of metastasis, was 40.6 months (95% CI, 35.5–48.6). Overall survival was significantly better for those who received first-line treatment (48.6 months, 95% CI 39.1- NR) than for those who received it in the second-line or beyond, p<0.0001 (Figure 2a), and in those who were treated with non-visceral metastasis (NR, 95% CI 40.6-NR), p<0.0001 (Figure 2b). Overall survival did not differ between the premenopausal and postmenopausal women (p=0.238), Figure 2c

In univariate analysis, the line of treatment (first-line or beyond), endocrine companion (AI versus fulvestrant), site of metastasis (visceral versus non-visceral), and timing of metastasis (de novo versus recurrent), but not menopausal status, were significantly associated with PFS and OS (Table-3). In multivariate analysis, line of treatment (first-line versus second-line and beyond [HR: 1.63, 95% CI 1.17–2.27, p=0.0039], endocrine companion (fulvestrant versus AI

Table 2 Treatment and Adverse Events

Variable	Level	Frequency	Percentage
Line of treatment (CDK4/6 inhibitors)	First line	227	63.8
	Second line	81	22.8
	Beyond	48	13.5
Endocrine treatment (with CDK4/6 inhibitor)	Aromatase Inhibitors (AI)	321	90.2
	Fulvestrant	35	9.8
Dose reduction	Never	255	71.6
	Yes	101	28.4
Neutropenia (required dose-reduction)	No	280	78.7
	Yes	76	21.3
Elevation of liver enzymes	No	335	94.1
	Yes	21	5.9
Cardiac adverse events	No	339	95.2
	yes	17	4.8
Status at last follow up	Alive	195	54.8
	Dead	161	45.2

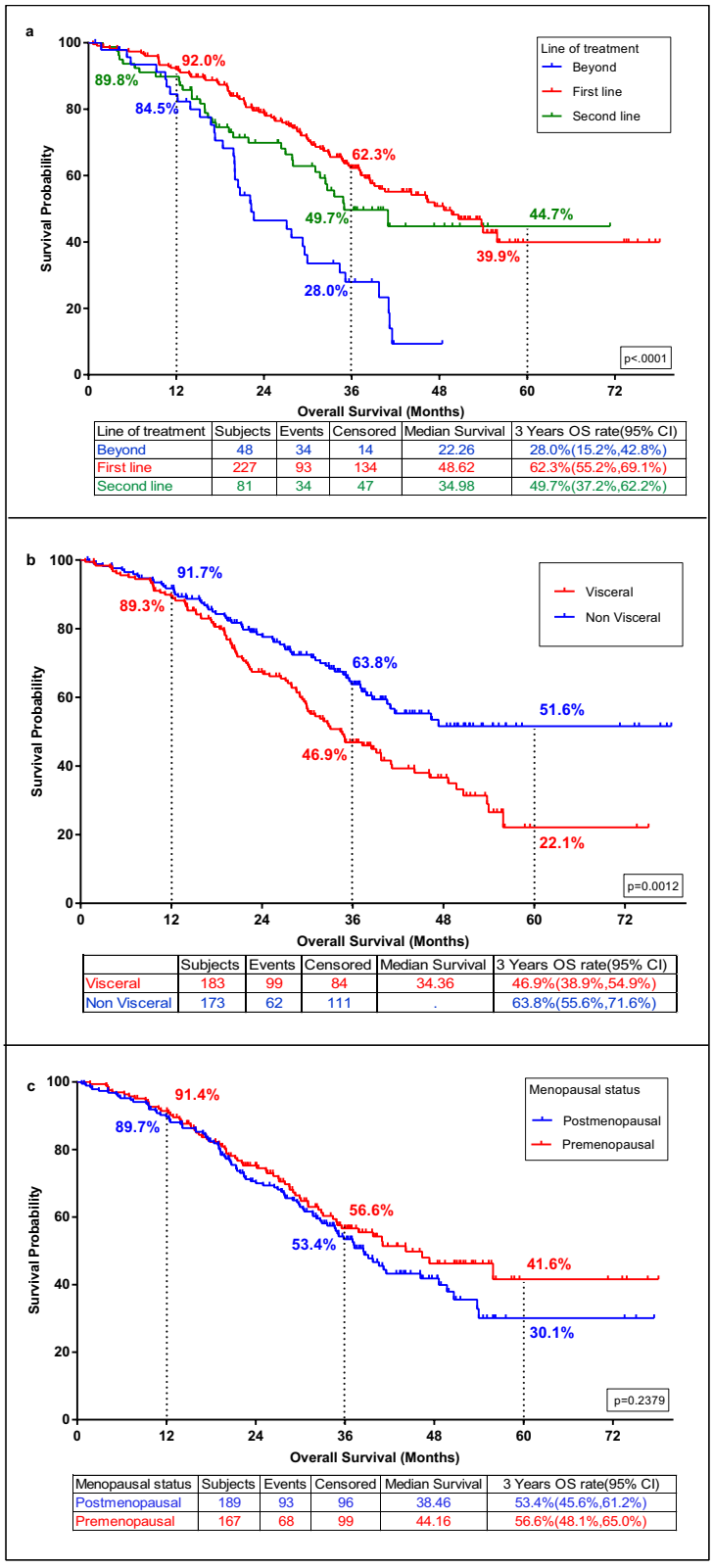


Line of treatment	Subjects	Events	Censored	Median Survival	3 Years PFS rate(95% CI)
Beyond	48	42	6	11.74	9.39%(2.61%,19.8%)
First line	227	122	105	32.13	49.2%(42.3%,56.2%)
Second line	81	47	34	25.74	35.6%(24.4%,47.7%)

	Subjects	Events	Censored	Median Survival	3 Years PFS rate(95% CI)
Visceral	183	128	55	19.44	31.2%(24.2%,38.7%)
Non Visceral	173	83	90	38.56	50.8%(42.7%,58.8%)

Menopausal status	Subjects	Events	Censored	Median Survival	3 Years PFS rate(95% CI)
Postmenopausal	189	122	67	25.25	37.7%(30.5%,45.3%)
Premenopausal	167	89	78	29.05	44.2%(36.1%,52.4%)

Figure 1 Progression-Free Survival (PFS) with rates (**a**) by treatment line (first line, second line, beyond), (**b**) by visceral versus non-visceral metastasis, and (**c**) by menopausal status (postmenopausal versus premenopausal).



Line of treatment	Subjects	Events	Censored	Median Survival	3 Years OS rate(95% CI)
Beyond	48	34	14	22.26	28.0%(15.2%,42.8%)
First line	227	93	134	48.62	62.3%(55.2%,69.1%)
Second line	81	34	47	34.98	49.7%(37.2%,62.2%)

	Subjects	Events	Censored	Median Survival	3 Years OS rate(95% CI)
Visceral	183	99	84	34.36	46.9%(38.9%,54.9%)
Non Visceral	173	62	111	.	63.8%(55.6%,71.6%)

Menopausal status	Subjects	Events	Censored	Median Survival	3 Years OS rate(95% CI)
Postmenopausal	189	93	96	38.46	53.4%(45.6%,61.2%)
Premenopausal	167	68	99	44.16	56.6%(48.1%,65.0%)

Figure 2 Overall survival with rates (**a**) by treatment line (first line, second line, beyond), (**b**) by visceral versus non-visceral metastasis, and (**c**) by menopausal status.

Table 3 Univariate Analysis for Both Overall Survival and Progression-Free Survival

Variable		Overall Survival (OS)			Progression Free Survival (PFS)		
		HR	95% Confidence Interval (CI)	p-value	HR	95% Confidence Interval (CI)	p-value
Line of treatment	Second line and beyond vs First line	1.82	1.327–2.497	0.0002	1.88	1.431–2.489	<0.0001
Endocrine treatment	Fulvestrant vs Aromatase inhibitors (AI)	2.709	1.745–4.208	<0.0001	2.567	1.714–3.843	<0.0001
Site of metastasis	Visceral vs non-visceral	1.684	1.226–2.314	0.0013	1.797	1.362–2.371	<0.0001
Menopausal status	Postmenopausal vs premenopausal	1.207	0.883–1.651	0.2381	1.268	0.964–1.666	0.0894
Timing of metastasis	Recurrent vs De novo	1.741	1.276–2.374	0.0005	1.706	1.302–2.236	0.0001

Table 4 Multivariate Analysis for Both Overall Survival and Progression-Free Survival

Variables		Overall Survival			Progression-Free Survival		
		Hazard Ratio	95% Confidence Interval (CI)	p-value	Hazard Ratio	95% Confidence Interval (CI)	p-value
Line of treatment	Second line and beyond vs First line	1.631	1.170–2.273	0.0039	1.798	1.353–2.389	<0.0001
Endocrine treatment	Fulvestrant vs Aromatase Inhibitors (AI)	2.001	1.262–3.172	0.0032	1.849	1.211–2.821	0.0044
Site of metastasis	Visceral vs non-visceral	1.539	1.117–2.122	0.0084	1.686	1.276–2.227	0.0002
Timing of metastasis	Recurrent vs De novo	1.677	1.222–2.301	0.0014	1.638	1.238–2.168	0.0005

[HR: 2.00,95% CI 1.26–3.17, p=0.0032], site of metastasis (visceral versus non visceral [HR:1.54, 95% CI 1.12–2.12, p=0.156], and timing of metastasis (recurrent versus de novo [HR: 1.68, 95% CI 1.22–2.30, p=0.0014] had a significant impact on OS (Table-4).

The 3-year PFS showed no significant difference between patients with dose reduction (45.0%, 95% CI: 34.9%–55.3%) and those with no dose reduction (38.8%, 95% CI: 32.4%–45.5%) (p = 0.3702). Similarly, the 3-year OS was comparable between those with dose reduction (57.5%, 95% CI: 46.9%–67.7%) and those with no dose reduction (53.8%, 95% CI: 46.9%–60.7%) (p = 0.2467) (Supplementary Figure).

Discussion

The last decade has witnessed remarkable progress in the treatment of breast cancer, mostly in patients with advanced-stage disease. It has been almost 10 years since the introduction of the first CDK4/6 inhibitor palbociclib in 2015 followed shortly by two other similar drugs, ribociclib and abemaciclib.[14] The introduction of these agents has changed the natural course of HR+/HER2- MBC. For the first time, we started to witness disease control after two years of endocrine therapy. The combination of AI or fulvestrant in the first-line setting or beyond, with any of the three approved CDK4/6 inhibitors, demonstrated statistically improved PFS compared to AI or fulvestrant alone. The recently published

follow-up data documenting an added overall survival advantage with ET, when combined with ribociclib, gave this particular CDK4/6 inhibitor an edge over the other two agents (palbociclib and abemaciclib); however, both were associated with better OS but were not statistically significant.[23]

Patients' experience with breast cancer, response and interaction with a particular treatment regimen may vary depending on age, race, ethnicity, disease status, genetic variation and comorbidities.[24] This is why it is essential that clinical trials include people with a variety of living conditions and lived experiences, as well as characteristics.[25] Additionally, treatment outcomes of patients in the "usual daily clinical practice" whether in academic institution or community practice, might not be the same as those performed under the very strict clinical trial settings.[26] Many of the adverse events associated with new drugs or treatment regimens can be more apparent and recognized after wider adoption and utilization. Such issues can be addressed and recognized using real-world data.[27] Our study illustrates an extremely important point; though, in a low-resourced country, like ours, and though CDK4/6 inhibitors were introduced at the center a little late after their FDA approval, but once integrated into clinical practice, we were able to reach similar treatment outcomes, both in efficacy and safety.

This retrospective study investigated real-world clinical outcomes of ribociclib plus ET (AI or fulvestrant) in patients with HR+/HER2- MBC treated at a single cancer center in a patient population that was poorly represented in clinical trials addressing this issue. Treatment efficacy, presented as PFS (median 27.3 months), and adverse events encountered in our study were similar to the published data. As expected, the median PFS of patients who had received ribociclib in combination with either letrozole or fulvestrant in the first-line setting (32.1 months) was significantly longer ($p<0.0001$) than that of patients who received the same treatment combination as a second line (25.7 months) or beyond (11.7 months).

The MONALEESA trial program assessed ribociclib in multiple Phase III clinical trials.[28] In patients with HR+, HER2– MBC, ribociclib + ET demonstrated consistently superior clinical benefit compared with ET alone, including significant improvement in overall survival (OS) in both premenopausal (MONALEESA-7)[29] and postmenopausal women (MONALEESA-3 and MONALEESA-2).[30–33]

Premenopausal Patients

Most clinical trials of CDK 4/6 inhibitors with AI or fulvestrant have mainly included postmenopausal patients and only a small subset of premenopausal patients on ovarian suppression. However, the phase III MONALEESA-7 trial enrolled 672 pre- or perimenopausal patients with HR-positive, HER2-negative, advanced breast cancer who were randomized to receive first-line treatment with either a non-steroidal AI, goserelin, tamoxifen plus ribociclib, or placebo. Compared with placebo, the addition of ribociclib was associated with better PFS (median PFS, 24 vs 13 months; HR 0.55, 95% CI 0.4–0.69). Similar observations were noted among the 167 premenopausal women included in our study, where a PFS of 29.1 months (95% CI 21.9–50.3) was observed.

Fulvestrant + CDK 4/6 Inhibitor

The phase III trial, MONALEESA-3, enrolled 726 patients with advanced HR-positive breast cancer treated with ribociclib or placebo with fulvestrant. The patients included two cohorts: those who had no prior endocrine therapy, and those who had disease progression on prior therapy. The combination of ribociclib and fulvestrant showed significant improvement in PFS compared to fulvestrant alone (21 vs 13 months; HR 0.59, 95% CI 0.48–0.73).[34] The benefit in PFS was seen in both cohorts; with and without prior endocrine treatment. In a subsequent analysis, a significant improvement in OS was observed.[32] In our study, because of late approval of the drug, only 35 (9.8%) of our cohort were treated with fulvestrant, and all were in second-line or beyond. The PFS (24.1, 95% CI 15.9–33.6) was similar to the 21 months reported in the MONALEESA-3 study. Ribociclib in combination with letrozole was also used as a first-line therapy in a phase III study (MONALEESA-2) in postmenopausal patients (n=668) with HR-positive, HER2-negative stage IV breast cancer.[33] At a median follow-up of 26.4 months, an improvement in PFS (25.3 vs 16.0 months, 95% CI 0.45–0.70) was observed. Our results in patients treated with ribociclib and AI as first-line therapies were similar to those obtained using MONALEESA-2.

The adverse events encountered, dose reduction, and discontinuation rates in our study were within those expected and observed in published clinical trials. No unusual cardiac or hepatic toxicity was observed. Both elevation of liver enzymes and prolongation of the QT interval were within previously reported rates.

In a previous study, our group reported no significant or unusual increase in the incidence of venous or arterial thromboembolism in patients treated with ribociclib in the first- or second-line settings. However, we reported two unique observations that may be linked to ribociclib; the first was for a patient who developed cerebral venous sinus thrombosis (CVST) in a patient treated with ribociclib with AI for metastatic breast cancer.[35] The second was vitiligo-like lesions in a patient treated with ribociclib and AI.[36]

Several studies were conducted to address treatment outcomes of CDK4/6 inhibitors in real-world settings. In one recently published study, researchers from Germany presented their data on 448 patients treated with palbociclib (71%), ribociclib (25%) or abemaciclib (3%). The median PFS was 17 months and dose reduction was performed in 30%, while 13% discontinued the treatment due to side effects.[37] In another retrospective study, 340 Taiwanese patients with HR-positive advanced breast cancer were treated with ribociclib and palbociclib. The median PFS for the whole cohort was 29 months and was almost similar in patients treated with palbociclib or ribociclib. Among the whole group, 66 (19%) progressed within the first 12 months of therapy and were considered resistant to CDK4/6 inhibitors.[38] The emergence of artificial intelligence (AI) should help real-world data extraction across the globe and should help disseminate knowledge and experience much faster and at a bigger scale on larger group of patients with different ethnicities and backgrounds. Researchers from Canada illustrated the feasibility of this approach in a relatively small study on patients treated with CDK4/6 inhibitors.[39]

Our study had some limitations. First, this was a retrospective study involving patients from a single center. Second, compared to strict data collection and reporting in prospective clinical trial settings, under-reporting of adverse events in patients' medical records may be considered.

Since more than half of the patients receiving fulvestrant were administered it as a second line or beyond, this could act as a confounder in the comparison between first line and beyond treatments. However, the multivariate analysis adjusts for these factors, helping to mitigate the confounding effect. Finally, given the retrospective nature of our study, we did not include a control group of patients who had received endocrine therapy alone.

Conclusion

In conclusion, in real-world settings and away from the strictness of controlled clinical trials, endocrine therapy in combination with CDK4/6 inhibitors (ribociclib in our study) in patients with HR-positive/HER2-negative MBC is an effective and well-tolerated therapy, with manageable toxicity profile and low drug discontinuation rates.

Disclosure

The authors report no conflicts of interest in this work.

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