RESEARCH ARTICLE

Comparing Ribociclib versus Palbociclib as a Second Line Treatment in Combination with Fulvestrant in Metastatic Breast Cancer: A Randomized Clinical Trial

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Abstract

  Aim: Assessment of CBR, PFS, QOL and toxicity profile of palbociclib and ribociclib. **Methods:** This is an interventional concurrent randomised phase III open label clinical trial. It took place at the Oncology Centre Mansoura University, Egypt from July 2022 till December 2023. Patients with pathologically proved ER+ HER2- metastatic breast cancer who either progressed on adjuvant hormonal or progressed on 1st line hormonal for metastatic disease. Patients in arm A received palbociclib 125 mg/day orally for 3 weeks and 1 week rest, plus fulvestrant. Patients in Arm B received ribociclib at a dose of 600 mg, administered orally once daily for 3 weeks and 1 week rest, plus fulvestrant. Pre- and peri-menopausal women received the LHRH agonist goserelin. Patients who lost their endorsement and were considered to be lost to follow up. Quality of life was analysed using the (EORTC) quality-of-life questionnaire (QLQ)-C30 V3.0. Patients were asked to complete the questionnaires at screening; at the 2nd and 6th month. Toxicity was assessed and graded using (CTCAE) v5.0. Patients were evaluated clinically for response and toxicity monthly and radiologically by CT and tumor markers/ 3 months. Treatment continued until objective Progressive Disease (PD), symptomatic deterioration, unacceptable toxicity or death. **Results:** Both arms had similar baseline characteristics. There was no statistically significant difference regarding the CBR (58.6% for both arms at 6 months and 13.8% in the palbociclib VS 17.2% in the ribociclib arm at 12 months). The median PFS to the whole population was 13 months. COX multivariate analysis revealed that postmenopausal had 2.85 more likely to survive than premenopausal patients. Patients with ECOG performance status 2 and 3 are 0.13 and 0.39 less likely to survive compared to patients with PS 1. Dose reduction increased the likelihood of survival 3.36 compared with no dose reduction. The median PFS was 13.67 months in the palbociclib arm and 12.69 months in the ribociclib arm with no statistically significant difference. During follow up, there was statistically significant improvement in insomnia in both arms and constipation in the palbociclib arm alone. Comparing the two arms, no statistically significant deterioration in the QOL domains except in fatigue and financial difficulties, with more deterioration in the palbociclib arm. Regarding common toxicities there was no statistically significant difference between the 2 arms. **Conclusions:** Both Ribociclib and palbociclib have similar CBR, PFS and toxicity profile.

Keywords: Cyclin dependent kinase- Ribociclib- Palbociclib- clinical trial- progression free survival- quality of life

Introduction

Breast cancer is the most common diagnosed cancer in females with estimated incidence of 2,3 million cases in 2020 and the 5th leading cause of death as well with mortality of 685,000 deaths worldwide. In Egypt, it is the most common cause of cancer mortality in women according to GLOBOCAN 2020 [1]. Approximately 6% of breast cancer patients are metastatic at the time of diagnosis, while 30% will develop metastasis after curative treatment for localised illness [2]. Stage IV breast cancer is an incurable disease [3]. Aromatase inhibitors (AIs) like letrozole, anastrozole, or exemestane, selective oestrogen receptor down-regulators (SERDs) eg fulvestrant, and selective oestrogen receptor modulators (such as tamoxifen) are the mainstay of anticancer endocrine therapy (ET) for hormone receptor positive Her2 negative disease [4]. Single agent tamoxifen or aromatase inhibitors show limited clinical benefit. They give the patients PFS ranging from 5 to 16 months [5]. But due to acquired resistance to hormonal therapy, new approaches are needed [6]. Cyclin dependent kinase

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inhibitors (CDK inhibitors) are a novel drug class approved a few years ago for treatment of hormone receptor positive, HER2 negative advanced breast cancer in the 1st line and subsequent lines in combination with aromatase inhibitors or fulvestrant. Studies showed that they extend progression free survival and recently they showed overall survival benefit [7]. The different types of CDK 4/6 inhibitors have similar mechanisms of action but they differ pharmacologically. They act by decreasing the viability of malignant cells by inhibiting CDK4/6 which results in blocking the phosphorylation of retinoblastoma protein, making the cell arrest at G1 phase [8]. The efficacy and comparative toxicity of Palbociclib and Ribociclib were indirectly compared in a number of trials [7], but not much was done to directly compare those agents. Moreover, this category of drugs is new to the Egyptian population, we know nothing about its efficacy, toxicity and quality of life. That is what this study is aiming for.The primary objectives are to compare the clinical benefit rate (CBR), quality of life and toxicity profiles of Ribociclib and Palbociclib. Secondary objectives were assessment of Progression free survival and Overall survival.

Materials and Methods

Study setting

The study took place at the Oncology Centre Mansoura University (OCMU), Egypt from July 2022 till December 2023. OCMU is the largest cancer centre in the delta region and serves thousands of patients every week.

Study design

It is an interventional concurrent randomised phase III open label clinical trial. Allocation ratio is 1:1.

Target population

Metastatic hormone receptor positive her2 negative breast cancer either progression on adjuvant hormonal or progression on 1st line hormonal for metastatic disease.

Inclusion criteria

Pathologically proven diagnosis of adenocarcinoma of the breast with evidence of metastatic disease either progression on adjuvant hormonal or progression on 1st line hormonal for metastatic disease, documentation of ER-positive and/or PR-positive and HER2 negative, prior use of endocrine therapy, age >18 years old and ECOG of 0 to 2.

Exclusion criteria

Patients with advanced/metastatic, symptomatic, visceral spread(visceral crisis) , that are at risk of life-threatening complications in the short term (including patients with massive uncontrolled effusions [pleural, pericardial, peritoneal], pulmonary lymphangitis, and over 50% liver involvement), 2nd malignancy other than breast cancer and patients with ECOG more than 3.

Sample size calculation

Sample size was calculated using Medcalc 15.8 (https://www.medcalc.org/). The primary outcome of interest is the overall response rate (ORR). Previous studies found ORR was 55% in Ribociclib (MONALEESA 2) and 25% in Palbociclib (PALOMA 3). With an alpha error of 5% and study power of 80% and 20% to compensate for drop out, then the sample size is 58 patients per group at least.

Methods of randomization

Legible patients were randomised into either arm using 29 blocks with block size of four. Randomization method was done with opaque sealed envelopes.

Data collected include

Age, Performance status, Comorbidities (DM, hypertension, HCV), menopausal status, pathology, site of metastasis, history of prior chemotherapy,type and grade of toxicity the patient developed, Dose reduction done for the patient.

Outcome measurement

This study included patients who received CDK inhibitors in the 2nd line setting. In Arm A patients received palbociclib 125 mg/day orally for 3 weeks and 1 week rest, plus fulvestrant. Patients in Arm B received ribociclib at a dose of 600 mg, administered orally once daily for 21 consecutive days, followed by 7 days off, plus fulvestrant. In both arms, pre- and peri-menopausal women also received the LHRH agonist goserelin (Zoladex® or generic). Patients who lost their endorsement and were considered to be lost to follow up. Quality of life was analysed using the European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire (QLQ)-C30 V3.0 [9] . Patients were asked to complete the questionnaires at screening; every 8 weeks for 6 months. Toxicity was assessed and graded using Common Terminology Criteria for Adverse Events (CTCAE) v5.0 [10]. Patients were evaluated clinically for response and toxicity monthly and radiologically by CT and tumor markers every 3 months. Clinical benefit rate was defined as the total number (or percentage) of patients who achieved a complete response, partial response, or had stable disease by CT assessment. Patients continued to receive assigned treatment until objective Progressive Disease (PD), symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurs first. postmenopausal is defined as: age>60 years old or < 60 years old with cessation of menstruation for at least 12 months and FSH or E2 in postmenopausal range or patients who underwent bilateral oophorectomy. Premenopausal is defined if not meeting the criteria of postmenopausal. They are obligated to receive LHRH agonist with their treatment. Endocrine sensitivity is defined in cases who progressed after more than 1 year after finishing adjuvant hormonal therapy. Cases are considered primary endocrine resistance when they progress within 6 months of endocrine therapy. If they progress after 6 months of endocrine therapy they are considered secondary resistant.

Ethical consideration

Study protocol was approved by the IRB committee of faculty of medicine Mansoura university, code number MD.22.07.674. Approval of the managers of the hospital

in which the study was conducted. Permission to use the EORTC QOL score BR-23 Arabic was obtained from the EORTC QOL group website. Informed verbal consent was obtained from each participant sharing in the study. Confidentiality and personal privacy was respected in all levels of the study. Collected data was not used for any other purpose.

Statistical analysis

Statistical analysis was performed using SPSS for Windows, version 22.0 (IBM Corporation, NY, USA). First, univariate analysis was performed to compare groups: chi-squared tests were used for categorical variables. Second, multivariate COX regression models were used for adjusting confounding factors while determining possible risk factors. A two-sided P-value <0.05 was considered statistically significant.

Registration number

This trial is registered at clinicaltrials.gov. Registration number ID: NCT05670054.

Results

Table 1 shows that age, sex, menopausal and performance status, comorbidities, pathological features, site of metastasis, endocrine sensitivity as well as history of prior chemotherapy received in the advanced setting were matched between the two arms with the exception of HCV positive status (20.6% were HCV positive in the palbociclib arm while only 6.9% in the ribociclib arm). Regarding the clinical benefit rate (CBR) -which is defined as the total number (or percentage) of patients who achieved a complete response, partial response, or had stable disease- there was no statistically significant

Table 1. Comparison of Clinicopathologic Baseline Characteristics between the 2 Arms

	Palbociclib N(%)	Ribociclib N(%)	P
Total	58 (100)	58 (100)	
Age/years (mean± SD)	55.44±11.37	52.34±11.75	0.15
Sex			1
Male	2 (3.4)	1 (1.7)	
Female	56 (96.6)"	57 (98.3)	
Menopausal status in females			0.76
Premenopausal	23 (41.1)	25 (43.9)	
Postmenopausal	33 (58.9)	32 (56.1)	
Method of induction of menopause in premenopausal			0.6
Zoladex	21 (91.3)	24 (96.0)	
Oophorectomy	2 (8.7)	1 (4.0)	
DM	17 (29.3)	13 (22.4)	0.4
HTN	18 (31.0)	18 (31.0)	1
HCV positive	12 (20.6)	4 (6.9)	0.03
ECOG Performance status:			0.79
1	43 (74.1)	42 (72.4)	
2	11 (19.0)	10 (17.2)	
3	4 (6.9)"	6 (10.3)	
Pathology grade			0.07
GI	1 (1.7)	0	
II	51 (87.9)	42 (72.4)	
III	6 (10.3)	14 (24.1)	
lobular	0	2 (3.4)	
Estrogen receptor (ER)[median(min-max)]	8 (0-8)	8 (2-8)	0.73*
Progesterone receptor (PR)[median(min-max)]	7 (0-8)	8 (2-8)	0.66*
HER2			1
Negative	31 (53.4)	31 (53.4)	
Low(+1 or +2 but ISH -ve)	27 (46.6)	27 (46.6)	
KI67			"0.56
≤20	21 (36.8)	15 (30)	0.45"
>20	36 (63.2)	35 (70)	
Site of metastasis:			"0.22
Bone only	12 (20.7)	10 (17.2)	0.63"
Visceral ± bone	46 (79.3)	48 (82.8)	
Endocrine therapy sensitivity:			0.57
Hormonal sensitive	6 (10.3)	3 (5.2)	
Primary hormonal resistance	18 (31.0)	18 (31.0)	
Secondary hormonal resistance	34 (58.6)	37 (63.8)	
Prior chemotherapy received in the advanced setting	19 (32.8)	18 (31.0)	0.84

Table 2. Comparing Response between the 2 Groups

	Palbociclib n=58 (%)	Ribociclib n=58 (%)	Significance P
Clinical benefit rate at 3 months	53 (91.4)	49 (84.5)	0.25
Clinical benefit rate at 6 months	34 (58.6)	34 (58.6)	
Clinical benefit rate at 9 months	14 (24.1)	22 (37.9)	0.1
Clinical benefit rate at 12 months	8 (13.8)	10 (17.2)	0.79

difference regarding the clinical benefit rate (58.6% for both arms at 6 months and 13.8% in the palbociclib VS 17.2% in the ribociclib arm at 12 months) (Table 2).

Regarding the quality of life scoring there were statistically significant baseline differences between the two arms. There was higher baseline physical functioning and global health scores in the ribociclib arm. On the other hand, higher scores of financial difficulties, fatigue and constipation in the palbociclib arm. During follow up, there was statistically significant improvement in insomnia in both arms and constipation in the palbociclib arm alone. Comparing the two arms, no statistically significant deterioration in the QOL domains except in fatigue and financial difficulties, with more deterioration in the palbociclib arm (Table 3).

Regarding common toxicities including cytopenia, GIT, cardiac, skin toxicities, headache, cough and lung disease there was no statistically significant difference between the two arms (Table 4). Twelve percent of palbociclib patients and 15.5% of the ribociclib patients had dose reduction due to toxicity. As the next line after progression on CDK Is, 12% of the patients in the palbociclib arm received chemotherapy and 24% received everolimus while in the ribociclib arm 13.7% and 34.4% received chemotherapy and everolimus respectively. By the end of follow-up 43.1% in the palbociclib arm and 46.5% of the ribociclib arm progressed on treatment, most commonly with visceral disease. About 79.31% of the palbociclib arm and 74.13% of the ribociclib arm were

alive at the last follow up (Table 5).

Overall survival was still immature and the median OS was not calculated. The median PFS to the whole population was 13 months. Considering the clinicopathologic characteristics, factors that impacted PFS were the menopausal status (better PFS in post menopausal patients 21 months VS 9 months in premenopausal patients, ECOG performance status with P value of 0.005 and endocrine sensitivity. Survival in patients with bone metastasis only was better than visceral metastasis (22 months VS 10 months with P value of 0.008). While other factors such as history of prior chemotherapy, endocrine therapy, pathological grade, level of HER2 and KI67 didn't have an impact on PFS (Supplementary Table 6). PFS was 10 months in patients who didn't have dose reduction while it was 21 months in patients who underwent dose reduction due to toxicity. PFS was not affected by the site of progression or the subsequent line after progression (Supplementary Table 7).

COX multivariate analysis revealed that postmenopausal had 2.85 more likely to survive than premenopausal patients. Also patients with ECOG performance status 2 and 3 are 0.13 and 0.39 less likely to survive compared to patients with PS 1. Dose reduction increased the likelihood of survival 3.36 compared with no dose reduction (Supplementary Table 8). The median PFS was 13.67 months in the palbociclib arm and 12.69 months in the ribociclib arm with no statistically significant difference. While PFS was similar in premenopausal
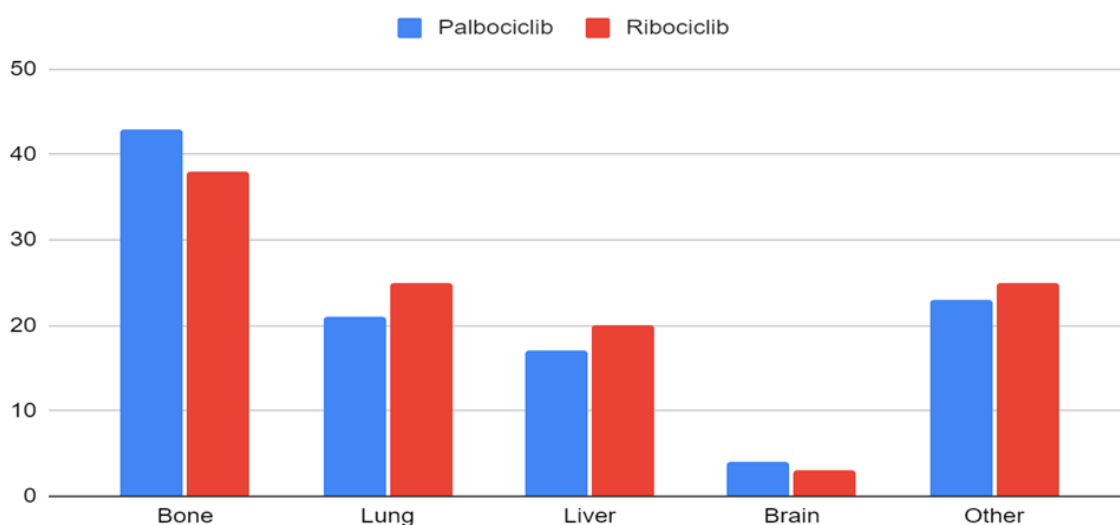

Figure 1. Site of Metastasis Including Bone, Lung, Liver, Brain and Other Sites. Blue bars are Palbociclib, red bars are Ribociclib. It is balanced between both groups.

Table 3. Comparison of Quality of Life Domains during Follow up between Studied Groups

Quality of life		Palbociclib n=58	Ribociclib n=58	p
Role limitation	Baseline	50 (0-100)	66.67 (0-100)	0.49
	FU1	66.7 (0-100)	66.67 (0-100)	0.91
	FU2	66.7 (0-100)	66.67 (0-100)	0.47
Friedman test , p value		0.24	0.28	
Physical functioning	Baseline	46.67 (0-100)	73.33 (0-100)	0.014*
	FU1	60 (0-100)	53.33 (0-100)	0.56
	FU2	63.33 (0-100)	70 (20-100)	0.25
Friedman test , p value		0.83	0.38	
Emotional functioning	Baseline	58.33 (0-100)	58.33 (0-100)	0.84
	FU1	58.33 (0-100)	50 (0-100)	0.65
	FU2	66.7 (0-100)	66.7 (0-100)	0.82
Friedman test , p value		0.23	0.73	
Cognitive functioning	Baseline	66.7 (0-100)	66.7 (0-100)	0.70
	FU1	66.7 (0-100)	66.7 (0-100)	0.82
	FU2	83.33 (0-100)	66.7 (0-100)	0.12
Friedman test , p value		0.46	0.46	
Social functioning	Baseline	66.7 (0-100)	66.7 (0-100)	0.71
	FU1	66.7 (0-100)	66.7 (0-100)	0.88
	FU2	66.7 (0-100)	75 (0-100)	0.59
Friedman test , p value		0.98	0.77	
Fatigue	Baseline	66.7 (11.11-100)	44.44 (0-100)	0.03
	FU1	55.56 (0-100)	44.4 (0-100)	0.42
	FU2	50 (0-100)	33.3 (0-100)	0.036
Friedman test , p value		0.11	0.46	
Nausea and vomiting	Baseline	25 (0-100)	16.7(0-100)	0.06
	FU1	16.7 (0-100)	16.7(0-100)	0.75
	FU2	16.7 (0-100)	0(0-100)	0.62
Friedman test , p value				
Pain	Baseline	66.7 (0-100)	50 (0-100)	0.10
	FU1	50 (0-100)	50 (0-100)	0.42
	FU2	33.3 (0-100)	41.67 (0-100)	0.28
Friedman test , p value		0.16	0.67	
Dyspnea	Baseline	33.3 (0-100)	33.3 (0-100)	0.05
	FU1	33.3 (0-100)	33.3 (0—100)	0.80
	FU2	33.3 (0-100)	0 (0-100)	0.96
Friedman test , p value		0.21	0.08	
Insomnia	Baseline	66.7 (0-100)ab	33.3 (0-100)a	0.17
	FU1	33.3 (0-100)a	66.7 (0-100)ab	0.85
	FU2	33.3 (0-100)b	33.3 (0-100)b	0.54
Friedman test , p value		0.026*	0.026*	
Appetite loss	Baseline	66.7 (0-100)	33.3(0-100)	0.15
	FU1	33.3 (0-100)	66.7(0-100)	0.83
	FU2	33.3 (0-100)	33.3(0-100)	0.39
Friedman test , p value		0.4	0.83	
Constipation	Baseline	33.3(0-100)a	0 (0-100)	0.037*
	FU1	33.3(0-100)b	0 (0-100)	0.16
	FU2	0(0-100)ab	33.3 (0-100)	0.49
Friedman test , p value		0.037*	0.44	
Diarrhea	Baseline	0 (0-100)	0 (0-100)	0.83
	FU1	0 (0-100)	0 (0-100)	0.59
	FU2	0 (0-100)	0 (0-33.3)	0.26
Friedman test , p value		0.92	0.86	
Financial difficulties	Baseline	66.7 (0-100)	33.3 (0-100)	0.034*
	FU1	66.7 (0-100)	33.3 (0-100)	0.62
	FU2	33.3 (0-100)	0 (0-100)	0.02*
Friedman test , p value		0.44	0.48	
Global health status (QOL)	Baseline	41.67 (0-100)	62.5 (0-100)	0.004*
	FU1	50 (0-100)	50 (0-100)	0.51
	FU2	54.17 (0-100)	58.33 (0-100)	0.76
Friedman test , p value		0.07	0.56	

*statistically significant used test, Mann Whitney U test.

Table 4. Toxicity Grade among Studied Groups and during Follow up

	Palbociclib N(%)	Ribociclib N(%)	P
Nausea			0.35
No	40 (68.96)	33 (56.89)	
GI-GII	16 (27.58)	23 (39.65)	
GIII-GIV	2 (3.44)	2 (3.44)	
Vomiting			0.44
No	46 (79.31)	44 (75.86)	
GI-GII	9 (15.51)	13 (22.41)	
GIII-GIV	3 (5.17)	1 (1.72)	
Constipation			
No	42 (72.41)	43 (74.13)	
GI-GII	16 (27.58)	15 (25.86)	
GIII-IV	0 (0)	0 (0)	
Diarrhea			1
No	47 (81.03)	48 (82.75)	
GI-GII	9 (15.51)	9 (15.51)	
GIII-GIV	2 (3.44)	1 (1.72)	
Anemia			0.83
No	29 (50)	32 (55.17)	
GI-GII	24 (41.37)	22 (37.93)	
GIII-GIV	5 (8.62)	4 (6.89)	
Neutropenia			0.71
No	28 (48.27)	32 (55.17)	
GI-GII	19 (32.75)	15 (25.86)	
GIII-GIV	11 (18.96)	11 (18.96)	
Thrombocytopenia			0.1
No	51(87.93)	56 (96.55)	
GI-GII	1(1.72)	1 (1.72)	
GIII-GIV	6(10.34)	1 (1.72)	
High ALT			0.75
No	52 (89.65)	53 (91.37)	
GI-GII	6 (10.34)	5 (8.62)	
GIII-GIV	0 (0)	0 (0)	
High AST			0.34
No	45 (77.58)	49 (84.48)	
GI-GII	13 (22.41)	9 (15.51)	
GIII-GIV	0 (0)	0 (0)	
Fatigue			0.91
No	31 (53.44)	30 (51.72)	
GI-GII	23 (39.65)	22 (37.93)	
GIII-GIV	4 (6.89)	6 (10.34)	
Arthralgia			0.44
No	50 (86.20)	46 (79.31)	
GI-GII	8 (13.79)	10 (17.24)	
GIII-GIV	0 (0)	2 (3.44)	
Backache			1
No	43(74.13)	44 (75.86)	
GI-GII	14(24.13)	13 (22.41)	
GIII-GIV	1(1.72)	1 (1.72)	
Cough			0.56
No	42 (72.41)	39 (67.24)	
GI-GII	15 (25.86)	19 (32.75)	
GIII-GIV	1 (1.72)	0 (0)	
Headache			1
No	40 (68.96)	39 (67.24)	
GI-GII	18 (31.03)	18 (31.03)	
GIII-GIV	0 (0)	1 (1.72)	
Pruritis			1
No	44 (75.86)	44 (75.86)	
GI-GII	14 (24.13)	13 (22.41)	
GIII-GIV	0 (0)	1 (1.72)	

Table 4. Continued

	Palbociclib N(%)	Ribociclib N(%)	P
Rash			0.54
No	51 (87.93)	53 (91.37)	
GI-GII	7 (12.06)	5 (8.62)	
GIII-GIV	0 (0)	0 (0)	
Alopecia			0.5
No	47 (81.03)	44 (75.86)	
GI-GII	11 (18.96)	14 (24.13)	
GIII-GIV	0 (0)	0 (0)	
Long QT			1
No	57 (98.27)	56 (96.55)	
GI-GII	1 (1.72)	1 (1.72)	
GIII-GIV	0 (0)	1 (1.72)	
Lung disease			0.76
No	52 (89.65)	51 (87.93)	
GI-GII	6 (10.34)	7 (12.06)	
GIII-GIV	0 (0)	0 (0)	

patients in both arms, postmenopausal patients had better survival in the palbociclib arm(not reached VS 17 months, P=0.047). There was no statistical difference in PFS between the 2 arms regardless of the level of HER2, Ki 67, site of metastasis and history of prior chemotherapy (Supplementary Table 9).

Discussion

Cyclin dependent kinase inhibitors combined with ET are currently the standard of care treatment for metastatic breast cancer in both first and second line settings. Up till now no direct comparison had been done between different members of the CDK I family. This study aimed to compare efficacy and toxicity between palbociclib and ribociclib. Also to investigate their effect in the Egyptian population.

The patients baseline and disease characteristics were well balanced across treatment arms including age, menopausal and performance status, endocrine sensitivity and history of prior chemotherapy with the exception of HCV positive status (20.6% were HCV positive in the palbociclib arm while only 6.9% in the ribociclib arm) but that had no effect on the occurrence of liver toxicity.

Similar to PALOMA 3 [11], this study included both pre and postmenopausal patients (41% of the palbociclib arm and 43% of the ribociclib arm were premenopausal). In contrast, MONALEESA 3 recruited postmenopausal

Table 5. Post Treatment Factors

	Palbociclib N(%)	Ribociclib N(%)	P
Total number	58	58	
Need for dose reduction	7 (12.1)	9 (15.5)	0.59
level of dose reduction			0.75
0	51 (87.9)	49 (84.5)	
1	4 (6.9)	4 (6.9)	
2	3 (5.2)	4 (6.9)	
3	0	1 (1.7)	
Subsequent line			0.13
Chemotherapy	7 (12)	8 (13.7)	
Everolimus	14 (24.1)	20 (34.4)	
Number of subsequent lines			0.52
0	38 (65.5)	32 (55.2)	
1	16 (27.6)	21 (36.2)	
2	4 (6.9)	5 (8.6)	
Status at last follow up			0.7
Progression	25 (43.1)	27 (46.5)	
No progression	33 (56.9)	31 (53.4)	
Dead	12 (20.69)	15 (25.86)	0.51
Alive	46 (79.31)	43 (74.13)	
Site of progression			0.05
Bone	1 (1.72)	4 (6.9)	
Visceral	15 (25.86)	20 (34.48)	
Bone and visceral	9 (15.51)	3 (5.17)	

*statistically significant

patients only. 20% of the palbociclib and 17% of the ribociclib arm had bone only metastasis. That is more or less similar to PALOMA-3(25% of the patients had bone metastasis only) And MONALEESA-3 (21%) [12].

This trial showed that there was no statistically significant difference regarding the clinical benefit rate (58.6% for both arms at 6 months and 13.8% in the palbociclib VS 17.2% in the ribociclib arm at 1 year). This is higher than the RENATA real world data, where CBR was 37.5% [13]. In PALOMA-3 CBR was higher, in the asian population it was 70% and in non Asian it was 66% [14]. In MONALEESA-3 and 7 ORR was calculated which included patients who achieved Complete or partial responses not patients with stationary disease. It was 32.4% and 41% in MONALEESA-3 and 7 respectively [2]. The median PFS to the whole population was 13 months. Comparing the 2 arms, there was no statistically significant difference(13.67 months in the palbociclib arm and 12.69 months in the ribociclib arm). This was less than what was reported in the 2nd line cohort of MONALEESA 3 trial (26 months) [15], MONALEESA 7(23 months) [5] but it was better than PALOMA 3(9.5 months).

A real world data analysis from Asia showed PFS of 18.3 months [16]. And another retrospective analysis done in Spain of 33 patients treated with palbociclib in the 2nd line and 28 with ribociclib in the 1st line.The median PFS was 12.76 months in palbociclib and not reached in ribociclib [17]. A real world study compared ribociclib and palbociclib in the 1st line setting and showed PFS of 29 and 28 months of ribociclib and palbociclib respectively. OS was higher with palbociclib(38.0 months vs 33.9 months) [18]. Petrelli and his colleagues [7] indirectly compared the efficacy of the palbociclib VS ribociclib in the second line setting in combination with fulvestrant and showed that they were similar in PFS, HR and response rates.

These differences from the clinical trials are due to differences in the inclusion criteria. Our trial included patients who received prior chemotherapy in the advanced setting and patients with ECOG PS status of 2 or 3(about 27% of the patients) while MONALEESA-3 excluded those patients. MONALEESA-7 included patients who received a previous chemotherapy but not endocrine therapy in the advanced setting [2]. In PALOMA-3 only 1 previous line of chemotherapy in the advanced setting was allowed [14]. This study also had a higher percentage of patients with visceral metastasis (about 80%) while MONALEESA 3 only included 50%. In our trial the majority of patients had endocrine resistant disease (89.6% of the palbociclib arm and 94.8% in the ribociclib arm). Also pharmaco-ethnicity might explain the racial variety in anticancer medication because of allelic variations of genes that encode the metabolising enzymes.

As mentioned above about 40% of the study were premenopausal. Overall they had inferior PFS than postmenopausal patients (9 months vs 21 months, P 0.04). COX multivariate analysis revealed that postmenopausal had 2.85 more likely to survive than premenopausal patients. This contrasts PALOMA-3 - in which 20% of the patients were premenopausal- and had similar PFS

between pre and postmenopausal patients with similar HR [19]. If we indirectly compare MONALEESA-3 (all population postmenopausal) and MONALEESA-7 (all population premenopausal) MONALEESA 3 had higher PFS [2]. Comparing both arms of our trial, PFS was similar in premenopausal patients, while postmenopausal patients had better survival in the palbociclib arm(not reached VS 17 months, P=0.047).

PFS in patients who received prior chemotherapy in the advanced setting was numerically inferior (9 VS 17 months). This matches the PALOMA-3 (OS in chemonaive patients was 39 vs 24 months in patients with prior chemotherapy) [20]. A real world analysis from Asia showed that heavy pretreated patients had worse PFS [16].

Our study showed that patients' performance status has a significant impact on PFS, something that might not be evident in PALOMA and MONALEESA trials as they usually exclude those patients with PS higher than 1, but it usually shows in real world data. When correlating the level of HER2 with PFS in patients on CDK Is, no statistically significant difference in PFS in the whole population or in either arms. This is in line with what Douganiotis and his colleagues [21] reported in 2022. He reported numerically but not statistically significant difference in mPFS (3.35 years for HER2 0 tumours, 2.18 years for HER2 +1 tumours, 1.74 years for HER2 +2/ ISH-negative tumours).

This study showed that patients with bone metastasis only had better PFS than patients with visceral metastasis. While other factors such as history of prior chemotherapy, endocrine therapy, pathological grade and KI67 didn't have an impact on PFS.That is similar to what Low et al, 2022 showed that the presence of liver, bone and brain metastasis adversely impacted the PFS. Development of endocrine resistance is inevitable in patients who receive hormonal therapy. When stratifying patients into endocrine sensitive or resistant, endocrine sensitive patients had better PFS than endocrine resistant. This matched the findings in PALOMA-3 that showed that endocrine sensitive patients had longer PFS by 7.8 months than placebo arm while resistant cases had only 2.3 months longer [11]. MONALEESA-3 showed similar findings as well [2].

12% of patients in the Palbociclib arm and 15.5% of patients in the Ribociclib arm had their dose reduced due to toxicity. PFS was 21 months in patients who had dose reduction while it was 10 months in patients who didn't have dose reduction (Figure 1). This may be explained by the fact that the patients who develop side effects to the drug are also sensitive to its effect and tolerate it for long duration if they are properly dose reduced. In an Asian real world data 72% of the patients had dose reduction and it was not associated with poorer survival [16].

Regarding the overall survival in this trial, up till now is still immature. Longer follow up is needed. In the MONALEESA 3 trial after 64 months of follow up patients who received ribociclib in the second line had median OS of 39.7 and in MONALEESA 7 mOS was 58.7 months, while in PALOMA 3 the OS was 43.9 months VS 28 months in the placebo fulvestrant arm and was not statistically significant. As per the WHO, QoL is 'a

people's view of themselves, of their situation throughout everyday life, with regards to the way of life and worthy systems in which they live and corresponding to their objectives, assumptions, norms and concerns [22].

Quality of life in this trial was assessed using (EORTC) quality-of-life questionnaire (QLQ)-C30 V3.0 at baseline, 3 and 6 months. scoring there were statistically significant baseline differences between the two arms. A significantly worse baseline physical functioning and global health scores in the ribociclib arm. And worse baseline financial difficulties, fatigue and constipation in the palbociclib arm. During follow up, there was statistically significant improvement in insomnia in both arms and constipation in the palbociclib arm alone. Comparing the two arms, a statistically significant increase in fatigue and financial difficulties domains in the palbociclib arm at 6 months. Otherwise other QOL domains- including pain and global health status- had similarly maintained in both ribociclib and palbociclib arms.

Patients with MBC without visceral crisis receiving first-line treatment usually have a good QOL. In MONALEESA-2 EORTC QLQ-C30 and EORTC QLQ-BR23 were used while in PALOMA-2 investigators used FACT BREAST, General and EQ-5D questionnaires. In both trials there was a significant reduction in pain in the experimental arm and QOL was maintained from baseline and maintained throughout the treatment period specially in patients who didn't experience progression [23, 24]. Ribociclib in MONALEESA-7 had similar effects in addition to improving pain, fatigue, physical, emotional and social functioning [25]. In the second line, PALOMA-3 used EORTC QLQ-C30, EORTC QLQ-BR23 questionnaires for assessment. Palbociclib addition to fulvestrant led to a significant improvement in global HR-QoL scores (66.1 versus 63.0, P = 0.0313). Also improved emotional functioning and pain scores from the baseline. However, A decline in role functioning was observed in the palbociclib arm [26].

Even though palbociclib has a favourable toxicity profile, it has not shown a QoL improvement in trials evaluating its addition to ET. In the PEARL and Young-PEARL studies, however, palbociclib plus ET showed better HR-QoL outcomes and a better safety profile compared with capecitabine. Ribociclib determined more satisfactory results, particularly among premenopausal patients. Restricted information is accessible about HR-QoL among subjects treated with CDK4/6i in the real world. The greater part of the proof in this setting respects patients getting palbociclib, with a solitary report including subjects treated with any CDK4/6i. They had similar results to what was reported in the clinical trials without major changes [26]. An indirect comparison was done by [7] showed that the rate of quality of life deterioration and toxicities were also similar with the exception of higher rate of QT prolongation with ribociclib.

Regarding the toxicity profile, GIII or IV neutropenia occurred in nearly 19% of both arms, which is more than 3 folds lower than PALOMA-2, 3, 2.8 times lower than MONALEESA-2 and similar to the RENATA study [13]. 8.6% of the palbociclib arm and 6.9% in the ribociclib arm developed G III and IV anaemia, higher than what

was reported in MONALEESA-3 (3%) and PALOMA-3 (2.6%). Higher incidence of thrombocytopenia 10.3% occurred in the palbociclib arm vs 1.7% in the ribociclib arm. That is higher than PALOMA-3 (2.3%) and it was not reported in the MONALEESA-3 trial.

Non hematologic G III and IV were uncommon in both arms with fatigue having the highest incidence (5% and 6% in palbociclib and ribociclib arm respectively). Overall there was no statistically difference between the 2 arms regarding toxicity profile. There were no reported GIII and IV ALT or AST elevation, in contrast to PALOMA-3 and MONALEESA-3 reported incidence of 3% and 6.6% respectively. Long QT interval was reported in the Ribociclib arm in a similar incidence to MONALEESA-3 (about 3%) [11, 27]. Twelve percent of palbociclib patients and 15.5% of the ribociclib patients had dose reduction due to toxicity. That is lower in incidence than PALOMA-2 (36%) and PALOMA-3 (32%) [13]. As the next line after progression on CDK Is, a higher proportion of patients received chemotherapy in the Ribociclib arm (34.4% VS 12% in Palbociclib arm). By the end of follow-up 43.1% in the palbociclib arm and 46.5% of the ribociclib arm progressed on treatment, most commonly with visceral disease.That is in concordance with the RENATA trial [13]. About 79.31% of the palbociclib arm and 74.13% of the ribociclib arm were alive at the last follow up.

A pooled analysis of patients who received Ribociclib in the first line showed that 46% of the ribociclib patients underwent a dose reduction, mainly due to neutropenia. Outcomes were evaluated according to relative-dose intensity, and found that there were minimal differences in patients with lower dose intensity [22].

Chemotherapy, alone or in combination, was received as the first subsequent therapy by 205 of the 571 patients who discontinued trial treatment (130 of 362 patients [35.9%] in the ribociclib group and 75 of 209 patients [35.9%] in the placebo group). Estimates for the percentage of patients who had not yet received chemotherapy at 42 months were 56.4%

This study has strengths like being the first direct comparison between CDK agents. It gave us a clue about the efficacy and toxicity profile of this family of target therapy in the Egyptian population. It has some limitations that include small sample size and higher rate of loss to follow up in the ribociclib arm. Larger study and longer follow up is needed for further assessment.

Author Contribution Statement

Manar Hamed ahmed shaaban collected the cases and wrote the manuscript. Mohamed Ali Elbaiomy revised the results and discussion. Ahmed Eltantawy Eltantawy designed the study and revised the results, Abdel-Hady El- Gilany Abdel-Fattah performed the statistical analysis, Sameh Sayed Ahmed Shamaa supervised the work and revised the manuscript.

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Informed verbal consent was obtained from each participant sharing in the study. Confidentiality and personal privacy was respected in all levels of the study. Collected data was not used for any other purpose.

Availability of data

Data is available upon request.

Trial registration

This trial is registered at clinicaltrials.gov. Registration number ID: NCT05670054.

Conflict of interest

The authors have no conflict of interest.

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