

# Real Practice Evaluation of Cyclin Dependent Kinase 4/6 (CDK4/6) Inhibitors in Treatment from Hormone Receptor Positive (HR+)/Human Epidermal Growth Factor Receptor-2 Negative (HeR-2-) in Advanced Breast Cancer Patients

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## ABSTRACT

**Background:** As the most frequent cancer overall & the leading cause from cancer-related deaths among women, breast cancer is a major global public health concern. Clinical, morphological, & molecular therapy from breast cancer vary due to its complexity & heterogeneity. CDK 4/6 inhibitors are the mainstay therapy for hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer. We don't have enough data on the three (CDK) 4/6 inhibitors & how to chose them for specific patients. **Aim:** This study aimed to select the most effective treatment between three types of CDK4/6 inhibitors, reduce the possible toxicities may occur from the drugs & achieve maximum benefit from the drugs with hormonal receptor positive in advanced breast cancer in Ismailia. **Patients & methods:** A retrospective cohort study was conducted. Study conducted in Ismailia (Suez Canal university hospitals oncology center). Advanced hormone receptor-positive, HER2-negative breast cancer patients taking CDK4/6 inhibitors as first-line treatment who experienced progression & recurrence following previous endocrine therapy. Patients were monitored monthly for 18 months. Survival & toxicity at last follow-up. First clinic visits included a personal & clinical history and physical evaluation for research participants. This research involves 60 female metastatic breast cancer patients who were hormonal positive/her2 negative & monitored for 18 months for CDK4/6 inhibitor toxicity. **Results:** The results from this study showed the distribution from progression free survival (PFS), which Ribociclib was effective & well -tolerated with longer Progression free survival (PFS) from (79.9%) from patients who had received it, whereas progression free survival in patient who received Abemaciclib & Palbociclib after 18 months from follow up duration was (64.7% & 76% respectively). The difference between groups was statistically insignificant ( $p\text{ value} = 0.09$ ). Overall survival (OS) after 18 month duration among studied groups, was 95.2%, 66.7% & 100% in Ribociclib, Abemaciclib & Palbociclib groups, respectively illustrated which there was statistically significant difference between studied groups regarding Overall survival from breast cancer ( $p=0.043$ ). **Conclusion:** Ribociclib, abemaciclib, & palbociclib have been shown to slow disease progression & improve patient outcomes in hormone receptor-positive (HR+) & HER2-negative advanced breast cancer patients. All three medications are successful with endocrine therapy, but their toxicity profiles, dosage adjustment needs, & preferred hormonal therapy combinations affect clinical treatment choices.

**Keywords:** CDK4/6, HR+, HeR-, Breast Cancer.

## Introduction

Breast cancer (BC) is the most frequent malignancy worldwide & the leading cause to cancer deaths and mortality in women.

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Clinical, morphological, & molecular therapy from breast cancer vary due to its complexity & heterogeneity. Women die from breast cancer at a rate from 1 in 39. Breast cancer ranks second in women's cancer deaths behind lung cancer (2.5%). It is a growing illness burden which threatens women's health <sup>(1)</sup>.

Breast cancer is the most common female cancers in Egypt, with an age-specific incidence rate from 48.8/10. HR+ but HER2 negative breast cancer accounts for 75% from cases. ET, targeted therapy, & chemotherapy are the major treatments for HR+/HER2 metastatic breast cancer <sup>(2)</sup>.

CDK 4/6 inhibitors are the mainstay therapy for hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer. A Chinese research published expert agreement on CDK4/6 inhibitor adverse effects in breast cancer. Drugs which inhibit CDK4/6 are used to treat hormone receptor-positive breast cancer. Chinese authorities have authorized Palbociclib, Abemaciclib, & Ribociclib for breast cancer therapy.

CDK4/6 inhibitors can cause bone marrow suppression, gastrointestinal toxicities, liver malfunction, & skin, subcutaneous tissue responses. Chinese Society from Clinical Oncology (CSCO) Breast Cancer Expert Group summarized AE incidence, clinical symptoms, & grading <sup>(3)</sup>.

Some research examined medication effectiveness, potency but not toxicities, side effects. Hormone-based therapies are twice as effective with them. Three oral medicines are available: Palbociclib, Ribociclib, & Abemaciclib. Using Palbociclib, Ribociclib, & Abemaciclib as first-line treatment for this form from breast cancer is a game-changer. These drugs have the same mechanism from

action, but their effectiveness & safety differ slightly <sup>(4)</sup>.

This study was the first to import the adverse effects, toxicity pattern, progression-free survival, overall survival, & clinical benefit rate from three CDK4/6 inhibitors (Abemaciclib, Ribociclib, & Palbociclib). CDK4/6 inhibitors are generally well-tolerated; however they can induce adverse effects like any other medicine. The most common side effects include nausea, fatigue, diarrhea, neutropenia, anemia, leukopenia, & thrombocytopenia.

Other adverse effects include neutropenia & leukopenia. CDK4/6 inhibitor-induced neutropenia is fast reversible, unlike chemotherapy-induced neutropenia. CDK4/6 inhibitors affect bone marrow neutrophil precursors cytostatically, explaining this discrepancy <sup>(5)</sup>.

#### **Aim from the study:**

This study aimed to improve expected outcomes from different CDK4/6i & ameliorate the ideal choice of treatment & reduce the expected hematological and non-hematological toxicities that occur with CDK4/6 inhibitors patients with advanced HR positive & HER-2 negative in advanced breast cancer patients & refine the disease-free survival (DFS) & progression free survival time (PFS) & increase the time to progression.

#### **Patients & Methods:**

This retrospective cohort study design was carried out at (clinical oncology & nuclear medicine department at Suez Canal University hospital (SCU) in Ismailia city, Egypt from August 2023 to February 2025. The information gathered derived from the integrating from data from real patients & their medical records. Sixty patients with hormone-receptor-positive, HER2-

negative advanced breast cancer who had progression, relapse during previous endocrine therapy, Women aged >18 years with hormone-receptor-positive, HER2 negative in advanced breast cancer patients, patients with metastasis, with any menopausal status (pre-, perimenopausal women received a gonadotropin-releasing hormone agonist) were included in the study. While women in early breast cancer patients & other breast nonepithelial tumors, male patients with breast cancer were excluded from the study.

All patients were subjected to the following, full history, & medical examinations. Patients were followed up every month for 18 months. Toxicity & survival at the last follow-up date. Toxicity was assessed & documented following the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 at every patient visit from baseline until follow-up <sup>(6)</sup>. Dosage & administration from drugs was in combination with an aromatase inhibitor: (Ribociclib 600mg PO daily for 21 consecutive days followed by 7 days off treatment, Abemaciclib 150mg PO BID until disease progression, unacceptable toxicity & Palbociclib 125mg PO daily on days 1-21 from each 28 days cycle. Cumulative toxicity was assessed for each patient as a total number from toxicities (all grades) & as a total number from moderate, higher toxicities ( $\geq$  grade 2). Stronger toxicity was assessed for patients who received multiple courses. Dose reduction, therapy discontinuation, prior & subsequent therapy line was recorded. Progression free survival as defined by Response Evaluation Criteria in Solid Tumors version 1.1, & measured from the time from receiving CDK4/6i until progressive disease, death (whichever was earlier) <sup>(7)</sup>.

### Data analysis:

SPSS 26 was used for all statistical analyses. Quantitative variables were described using mean, SD, , percentages. Qualitative factors were described in diagrams & tables when relevant. Chi-square test for categorical variables & Student t-test/ANOVA for continuous variables with normally distributed data were used to examine associations. Category-specific Chi-square tests & continuous Mann-Whitney U/Kruskal Wallis tests were used to assess non-normally distributed data. Results were significant if  $p < 0.05$ .

### Results:

This is a retrospective cohort study which conducted on 60 female patients with advanced breast cancer HR positive & HER2 negative who attended at (Suez Canal university hospitals at oncology center) at Ismailia city. From the 60 patients whom, were included in the study 42, 12 & 6 patients received treatment with Ribociclib, Abemaciclib & Palbociclib, respectively combined with hormonal treatment aromatase inhibitor.

As shown in table 1 that there was no statistically significant difference between the studied groups regarding laterality from breast, while there was no statistically significant difference between the studied groups regarding age & tumor pathology. All patients who received Abemaciclib & Palbociclib were having Oligo metastatic disease, while 95.2% of patients who received Ribociclib were having oligo metastatic group. There was no statistically significant difference between studied groups regarding DM, HTN, DVT, & hyperthyroidism, while there

was a statistically significant difference between studied groups regarding valvular

disease. No one who received Palbociclib has chronic disease.

**Table 1: Distribution from patient characteristics data between the studied groups.**

|                        |                    | Ribociclib group<br>N= 42 |       | Abemaciclib group<br>N= 12 |        | Palbociclib group<br>N=6 |        | P value |
|------------------------|--------------------|---------------------------|-------|----------------------------|--------|--------------------------|--------|---------|
|                        |                    | mean                      | ±SD   | mean                       | ±SD    | mean                     | ±SD    |         |
| Age (year)             |                    | 56.02                     | ±9.7  | 57.75                      | ±9.8   | 47.5                     | ±11.6  | 0.1     |
|                        |                    | N                         | %     | N                          | %      | N                        | %      |         |
| Laterality from breast | Left               | 30                        | 71.4% | 7                          | 58.3%  | 4                        | 66.7%  | 0.08    |
|                        | Right              | 10                        | 23.8% | 4                          | 33.3%  | 2                        | 33.3%  |         |
|                        | Bilateral          | 2                         | 4.8%  | 1                          | 8.4%   | 0                        | 0%     |         |
| Metastasis             | Oligo metastasis   | 40                        | 95.2% | 12                         | 100%   | 6                        | 100%   | 0.64    |
|                        | Multi-metastasis   | 2                         | 4.8%  | 0                          | 0.0%   | 0                        | 0.0%   |         |
| Pathology              | Ductal             | 24                        | 57.1% | 8                          | 66.7%  | 4                        | 66.7%  | 0.18    |
|                        | Lobular            | 17                        | 40.5% | 2                          | 16.65% | 1                        | 16.65% |         |
|                        | Medullary          | 1                         | 2.4%  | 2                          | 16.65% | 1                        | 16.65% |         |
| Comorbidities          | DM                 | 9                         | 21.4% | 2                          | 16.7%  | 0                        | 0%     | 0.451   |
|                        | HTN                | 19                        | 45.2% | 4                          | 33.3%  | 0                        | 0%     | 0.013*  |
|                        | (Valvular disease) | 0                         | 0%    | 3                          | 25%    | 0                        | 0%     | 0.002*  |
|                        | DVT                | 1                         | 2.4%  | 0                          | 0%     | 0                        | 0%     | 0.804   |
|                        | Hyperthyroidism    | 1                         | 2.4%  | 0                          | 0%     | 0                        | 0%     | 0.804   |

Table 2 shows that, there was statistically significant difference between studied groups regarding hormonal drug

especially for liver & lung metastases. There was no statistically significant difference between studied groups regarding visceral crisis

Table3 shows that, Ribociclib group had a higher proportion from patients with visceral metastases compared to the other two groups,

**Table 2: Distribution from hormonal treatment combined with CDK4/6 I between the studied groups.**

|             | Ribociclib<br>Group N=42 |       | Abemaciclib group<br>N=12 |       | Palbociclib group<br>N=6 |       | P value |
|-------------|--------------------------|-------|---------------------------|-------|--------------------------|-------|---------|
|             | N                        | %     | N                         | %     | N                        | %     |         |
| Fulvestrant | 30                       | 71.4% | 3                         | 25%   | 2                        | 33.4% | 0.01*   |
| Exemestane  | 0                        | 0%    | 2                         | 16.7% | 0                        | 0     |         |
| Anastrozole | 4                        | 9.5%  | 3                         | 25%   | 2                        | 33.3% |         |
| Letrozole   | 8                        | 19.1% | 4                         | 33.3% | 2                        | 33.3% |         |

**Table 3: Distribution from visceral crisis between the studied groups.**

|                 |              | Ribociclib group N=42 |       | Abemaciclib group N=12 |       | Palbociclib group N=6 |       | P value |
|-----------------|--------------|-----------------------|-------|------------------------|-------|-----------------------|-------|---------|
|                 |              | N                     | %     | N                      | %     | N                     | %     |         |
| Visceral crisis |              |                       |       |                        |       |                       |       |         |
| Yes             | Liver        | 1                     | 2.4%  | 1                      | 8.3%  | 0                     | 0.00% | 0.71    |
|                 | Liver & lung | 2                     | 4.8%  | 0                      | 0.00% | 0                     | 0.00% |         |
| No              |              | 39                    | 92.9% | 11                     | 91.7% | 6                     | 100%  |         |

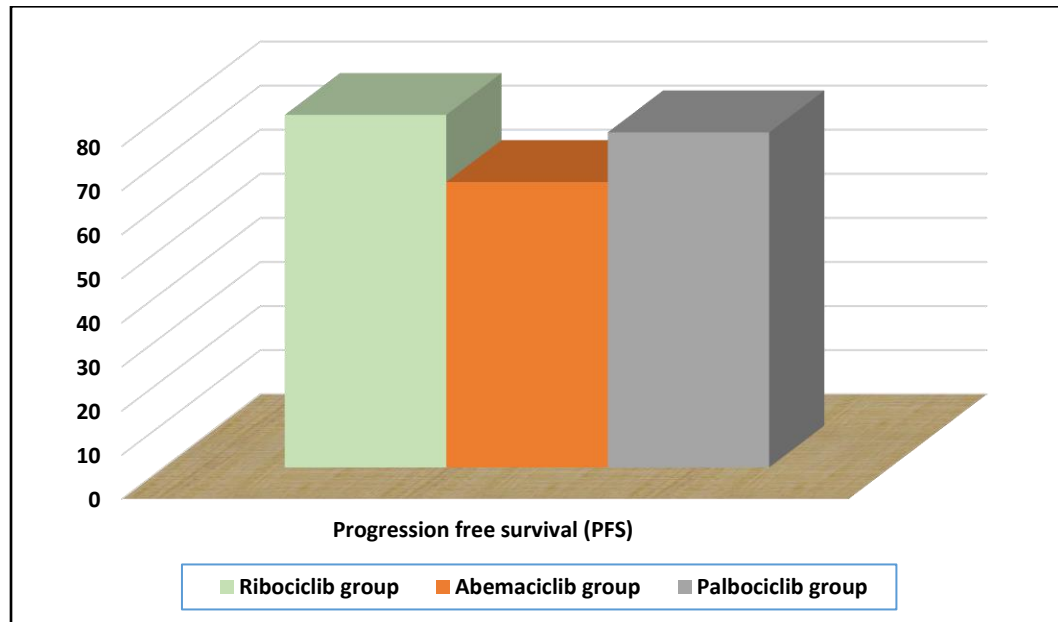


Figure 1: Distribution from Progression free survival (PFS) between the studied groups.

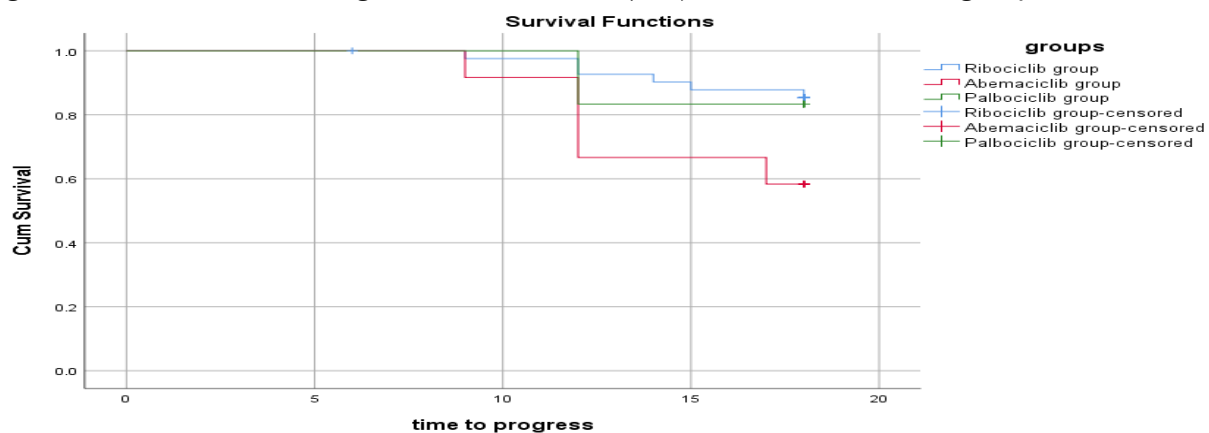


Figure 2: showed Kaplan-Meier curve for Ribociclib, Abemaciclib &amp; Palbociclib showed significant p value from 0.043.

Progression free survival after 18 month duration among studied groups illustrated which there was statistically insignificant

difference between studied groups regarding Progression free survival from breast cancer (p=0.09).

Overall survival after 18 month duration among studied groups was 95.2%, 66.7% & 100% in Ribociclib, Abemaciclib & Palbociclib groups respectively illustrated

which there was statistically significant difference between studied groups regarding Overall survival from breast cancer ( $p=0.043$ ).

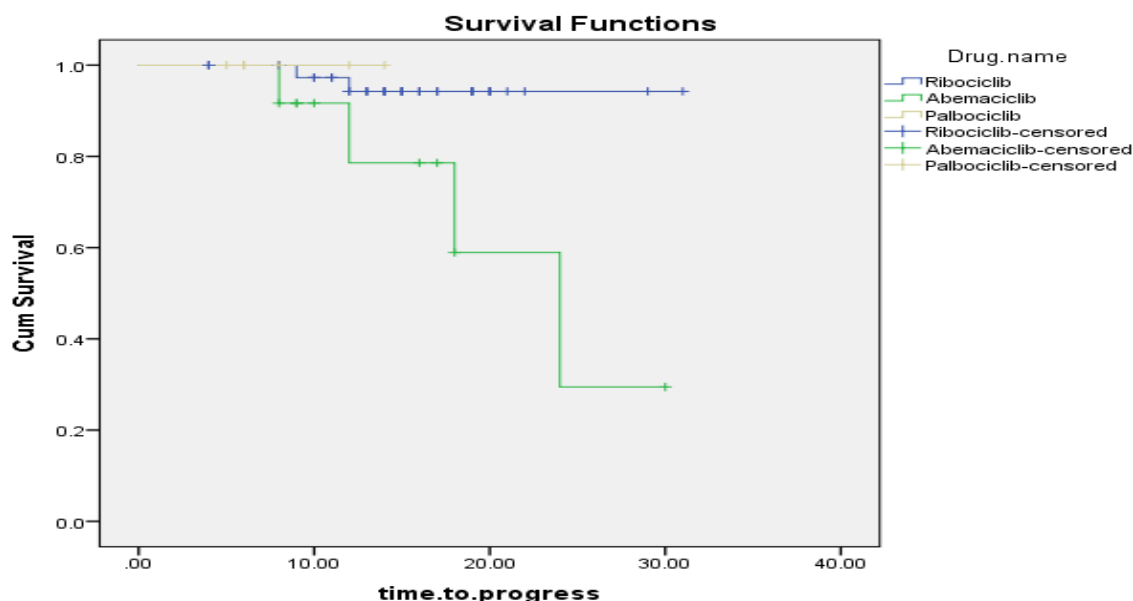


Figure 3: Kaplan-Meier curve for Ribociclib, Abemaciclib & Palbociclib showed insignificant p value from 0.09.

As shown in table 4 that, the ribociclib group showed a CR rate from 42.9%, while the abemaciclib group had a slightly higher rate from 50%, & the palbociclib group had a lower rate from 33.3%. The rates for partial response are fairly similar across the groups, with ribociclib at 28.6%, abemaciclib at 25%, & palbociclib at 16.7%. The ribociclib group had 9.5% from patients with stable disease, abemaciclib had 8.3%,

& palbociclib had no patients with stable disease. The ORR, was highest in the abemaciclib group at 75%, followed by ribociclib at 71.4%, & palbociclib at 50%. The clinical benefit rate, was highest in the abemaciclib group at 75%, followed by ribociclib at 73.8%, & palbociclib at 50%. There were some differences in response rates between the groups, but these differences were not statistically significant.

**Table 4: Distribution from Objective Response Rate (ORR) & Clinical Benefit Rate (CBR) between the studied groups.**

|                               | Ribociclib group<br>N=42 |       | Abemaciclib group<br>N=12 |      | Palbociclib group<br>N=6 |       | P value |
|-------------------------------|--------------------------|-------|---------------------------|------|--------------------------|-------|---------|
|                               | N                        | %     | N                         | %    | N                        | %     |         |
| Complete response             | 18                       | 42.9% | 6                         | 50%  | 2                        | 33.3% | 0.84    |
| Partial response              | 12                       | 28.6% | 3                         | 25%  | 1                        | 16.7% | 1       |
| Stable disease                | 4                        | 9.5%  | 1                         | 8.3% | 0                        | 0.0%  | 1       |
| Objective response rate (ORR) | 30                       | 71.4% | 9                         | 75%  | 3                        | 50%   | 0.51    |
| Clinical benefit rate (CBR)   | 31                       | 73.8% | 9                         | 75%  | 3                        | 50%   | 0.81    |

Table 5 shows that, there was statistically significant difference between studied groups regarding GIT toxicity. 23.8% from patients who received Ribociclib had GIT

toxicity, 58.3% from those who had received Abemaciclib had GIT toxicity & 66.7% from those who had received Palbociclib had GIT toxicity.

**Table 5: Distribution from GIT toxicity between the studied groups.**

|              | Ribociclib group<br>N=42 |       | Abemaciclib group<br>N=12 |       | Palbociclib group<br>N=6 |       | P value |
|--------------|--------------------------|-------|---------------------------|-------|--------------------------|-------|---------|
|              | N                        | %     | N                         | %     | N                        | %     |         |
| GIT toxicity |                          |       |                           |       |                          |       |         |
| Yes          | 10                       | 23.8% | 7                         | 58.3% | 4                        | 66.7% | 0.019*  |
| No           | 32                       | 76.1% | 5                         | 41.7% | 2                        | 33.3% |         |

**Table 6: Distribution from BM toxicity between the studied groups.**

|             | Ribociclib group<br>N=42 |       | Abemaciclib group<br>N=12 |       | Palbociclib group<br>N=6 |       | P value |
|-------------|--------------------------|-------|---------------------------|-------|--------------------------|-------|---------|
|             | N                        | %     | N                         | %     | N                        | %     |         |
| BM toxicity |                          |       |                           |       |                          |       |         |
| Yes         | 6                        | 14.3% | 4                         | 33.3% | 1                        | 16.7% | 0.32    |
| No          | 36                       | 85.7% | 8                         | 66.7% | 5                        | 83.3% |         |

**Table 7: Distribution from hematological & non-hematological toxicities between the studied groups.**

|                              |                    | Ribociclib group<br>N=42 |        | Abemaciclib group<br>N=12 |       | Palbociclib group<br>N=6 |       | P value |
|------------------------------|--------------------|--------------------------|--------|---------------------------|-------|--------------------------|-------|---------|
|                              |                    | N                        | %      | N                         | %     | N                        | %     |         |
| Hematological toxicities     |                    |                          |        |                           |       |                          |       |         |
| Anemia                       | Grade 1 (Mild)     | 3                        | 7.1%   | 1                         | 8.3%  | 1                        | 16.6% | 0.73    |
|                              | Grade 2 (Moderate) | 1                        | 2.4%   | 1                         | 8.3%  | 0                        | 0.0%  |         |
|                              | Grade 3 (Severe)   | 0                        | 0.0%   | 0                         | 0.0%  | 0                        | 0.0%  |         |
|                              | Total              | 4                        | 9.5%   | 2                         | 16.7% | 1                        | 16.6% |         |
| Thrombocytopenia             | Grade 1 (Mild)     | 1                        | 2.4%   | 0                         | 0.0%  | 0                        | 0.0%  | 0.804   |
|                              | Grade 2 (Moderate) | 0                        | 0.0%   | 0                         | 0%    | 0                        | 0.0%  |         |
|                              | Grade 3 (Severe)   | 0                        | 0.0%   | 0                         | 0%    | 0                        | 0.0%  |         |
|                              | Total              | 1                        | 2.4%   | 0                         | 0.0%  | 0                        | 0.0%  |         |
| Neutropenia                  |                    | 0                        | 0.0%   | 2                         | 16.7% | 0                        | 0.0%  | 0.015   |
| Neutropenic fever            |                    | 1                        | 2.4%   | 0                         | 0.0%  | 0                        | 0.0%  | 0.81    |
| Non-hematological toxicities |                    |                          |        |                           |       |                          |       |         |
| Vomiting                     |                    | 2                        | 4.8%   | 2                         | 16.7% | 2                        | 33.3% | 0.019*  |
| Diarrhea                     | Grade 1 (Mild)     | 4                        | 9.5%   | 3                         | 25%   | 1                        | 16.7% | 0.019   |
|                              | Grade 2 (Moderate) | 3                        | 7.1%   | 1                         | 8.3%  | 1                        | 16.7% |         |
|                              | Grade 3 (Severe)   | 1                        | 2.4%   | 1                         | 8.3%  | 0                        | 0     |         |
|                              | Total              | 8                        | 19.05% | 5                         | 41.7% | 2                        | 33.3% |         |
| ECG changes                  |                    | 3                        | 7.1%   | 1                         | 8.3%  | 0                        | 0.0%  | 0.77    |
| Vitiligo                     |                    | 1                        | 2.4%   | 0                         | 0.0%  | 0                        | 0.00% | 0.8     |
| Hair loss                    |                    | 7                        | 16.7%  | 2                         | 16.7% | 2                        | 33.3% | 0.61    |
| Lung injury (pneumonitis)    |                    | 2                        | 4.8%   | 1                         | 8.3%  | 0                        | 0%    | 0.74    |

Table 6 shows that, there was no statistically significant difference between studied groups regarding BM toxicity.

As shown in table 7, there was no statistically significant difference between studied groups regarding anemia, thrombocytopenia, neutropenia fever, vomiting, Diarrhea, ECG changes, vitiligo, hair loss & lung injury (pneumonitis). There was statistically significant higher in Abemaciclib group when compared to Ribociclib & Palbociclib groups regarding Neutropenia.

ECG changes which occurred with Ribociclib represented as QT prolongation & T-wave inversion but with normal cardiac enzymes & preserved EF in echocardiography.

## Discussion:

Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors added to endocrine therapy for advanced hormone receptor-positive & HER2-negative (HR+/HER2-) breast cancer patients have improved survival outcomes & become the first-line treatment. Some patients benefit more than others, & indicators from sensitivity & resistance are being sought <sup>(8)</sup>.

The median age from all female patients at diagnosis was 47 years, which was consistent with Saudi Arabia (45.7 years) & Asia (47.3 years) but lower than the US (60 years) <sup>(9)</sup>. These locations have a younger population than the US, which may be attributable to environmental & genetic causes. Breast cancer mostly affects middle-aged & older women. The median breast cancer diagnostic age is 62. This indicates half from breast cancer patients are under 62. Few breast cancer patients are under 45 <sup>(10)</sup>. The relationship between breast cancer laterality & hormonal & HER2 is still poorly understood, while other

clinicopathological aspects have been thoroughly studied. Cross-sectional, retrospective research from breast cancer laterality vs clinicopathological variables & prognosis in a specific ethnic community. A study examined 228 breast cancer patients treated at Arabian Gulf University in Bahrain from 1999 - 2020. Right-sided breast cancer was related with a higher positive family history from malignancy, a larger ratio from locally progressed & metastatic disease, & a worse 5-year survival relative to size & stage. Left-sided breast cancer had a greater early tumour stage <sup>(11)</sup>.

All patients provided age at diagnosis & family history. First-degree relatives with breast cancer were older & diagnosed later than second-/third-degree relatives. The cohort analysis found which family history from breast cancer predominantly affected age, tumour stage, & grade at diagnosis <sup>(12)</sup>. Research suggests a link between gender & sporadic breast cancer, particularly in those without family history <sup>(13)</sup>.

Regarding clinicopathological aspects from breast cancer & the most prevalent location from metastasis in advanced breast cancer, prior research used SEER data to analyse de novo metastatic breast cancer survival by metastatic site. Compared to non-metastatic breast cancer, metastatic breast cancer (MBC) has a poor prognosis. Breast cancer distant metastasis occurs in bone, liver, lung, & brain <sup>(14)</sup>.

Regarding the visceral crisis; Rugo et al. <sup>(15)</sup>revealed which Abemaciclib group had mild visceral metastases & somewhat improved brain metastases owing to BBB crossing. The palbociclib group had the fewest visceral metastases, which may have reduced its CR & CBR. Perrone et al. (2023) detected visceral



metastases in 69.5% from palbociclib, 78.7% from abemaciclib, & 78.1% from ribociclib patients.

In our study, 7.1% from 42 Ribociclib patients suffered visceral crisis, one from whom had liver & two had liver & lung. Our investigation confirmed which Palbociclib had the lowest proportion from visceral metastases, since Abemaciclib had just one patient with liver visceral crisis & Palbociclib could not monitor any patients with such crises.

National Health Insurance Service keeps national records from all covered inpatient & outpatient visits, & breast cancer was linked to leukemia, cardiomyopathy, osteoporosis, endometrial cancer, hypothyroidism, pulmonary fibrosis, myeloma, hyperlipidemia, & type 2 diabetes in the last large national cohort. Women with breast cancer had a higher incidence from leukemia & multiple myeloma. The risk for leukemia increased after breast cancer diagnosis & remained elevated even five years later. Hyperthyroidism is a major risk factor for changing body metabolism in adults & females from all races, ethnicities, & genders <sup>(16)</sup>.

Our study found 60.3% from people had comorbidities. Comorbidities including diabetes & hypertension were most common. 30.3% from women had hypertension. Diabetes & hypertension affect prognosis & outcomes together.

Our study sought to improve treatment options & quality from life for advanced HR positive & HER2 negative breast cancer patients. Combining hormonal treatment (fulvestrant, aromatase inhibitors with CDK4/6 inhibitor); Due to its established survival advantage in premenopausal women, Ribociclib is more routinely used with aromatase inhibitors (Als), according

to Perrone et al. <sup>(17)</sup>. Since palbociclib is the only CDK4/6 inhibitor licensed for monotherapy, it is typically used alongside Fulvestrant in endocrine-resistant individuals. The usage from Palbociclib with Als & Fulvestrant is balanced.

We found which Ribociclib & fulvestrant were the most common combination therapy, with 71.4% (about 30 patients), followed by Palbociclib & fulvestrant (33.4%), Abemaciclib & fulvestrant (25%), & Aromatase inhibitors (28.6%, 75%, & 66.7%). In this investigation, hormonal medication coupled with CDK4/6i showed statistically significant differences between groups.

In post- and premenopausal women with advanced HR-positive HER2-negative breast cancer, adding CDK4/6 inhibitors to endocrine therapy, either first-line, after progression to an aromatase inhibitor, increases progression-free survival. Past therapies, menopause, age, ductal, lobular histology, progesterone receptor status, and metastatic disease sites do not alter benefit. Palbociclib improved progression-free survival (PFS) in advanced HR+/HER-2 negative breast cancer postmenopausal women compared to letrozole monotherapy in PALOMA-2 and PALOMA-3 studies. Ribociclib outperformed letrozole and fulvestrant in advanced HR+/HER-2 negative breast cancer postmenopausal women <sup>(18)</sup>.

For overall survival (OS), Liu et al. <sup>(13)</sup> reported which ribociclib + fulvestrant was best (34.11%) & abemaciclib second (25.75%). Lin et al. <sup>(19)</sup> meta-analyzed six eligible trials to determine if CDK4/6 with AI, fulvestrant, ribociclib, abemaciclib with endocrine therapy extended OS as compared to endocrine therapy alone. Our study showed which overall survival (OS) after 18 months was 95.2%, 66.7%, & 100% in Ribociclib, Abemaciclib, & Palbociclib

groups, respectively, indicating a statistically significant difference in breast cancer overall survival ( $p=0.043$ ) & consistency with prior studies.

Fasching et al. <sup>(20)</sup> suggested which abemaciclib & ribociclib's greater CR rates improve long-term patient outcomes. Palbociclib, with the lowest CR rate, had the shortest OS (~53.9 months), suggesting its inability to achieve full tumor response may lead to worse survival outcomes.

We discovered which the ribociclib group had a CR rate from 42.9%, the abemaciclib group 50%, & the palbociclib group 33.3%. The clinical benefit rate was highest in the abemaciclib group (75%), followed by ribociclib (73.8%) & palbociclib (50%) Response rates differed across groups, although not significantly. In this research, abemaciclib & palbociclib required dosage reduction in cycle 2 & 3 more often (16.7%) than ribociclib (7.1%), with abnormal CBC & liver profile being the most prevalent explanation. Our investigation didn't find difference in progression-free & overall survival between dose decrease & full dosage individuals.

Jhaveri et al. <sup>(21)</sup> observed which CDK4/6i dosage reductions were needed in 108 patients (52.4%), 53.6% from abemaciclib patients, 52.1% from palbociclib patients, & 31.9% from ribociclib patients.

Chen et al. <sup>(22)</sup> discovered which abemaciclib patients had more all-grade diarrhea than the other two groups (12.66%, 0.00%, & 2.38%, respectively), consistent with its safety profile. Palbociclib with AI (53.98%) & fulvestrant (51.37%) had the greatest adverse event rates, according to Liu et al. <sup>(13)</sup>

This study showed no statistically significant difference between groups in anemia, thrombocytopenia, neutropenia

fever, & hematological toxicity. Abemaciclib (33.3%) had 16.7% anemia & 16.7% neutropenia, compared to Ribociclib (14.5%) (9.5% anemia, 2.4% thrombocytopenia, & 2.4% neutropenic fever) & Palbociclib (16.7%) (16.7% anemia, no neutropenia, fever).

Ribociclib caused hepatic, respiratory, & QTc prolongation, according to Onesti & Jerusalem <sup>(23)</sup>. Ribociclib causes QT prolongation & T-wave inversion, although abemaciclib & palbociclib do not. Routine ECG monitoring is needed to prevent major arrhythmias, & patients with cardiovascular risk factors, QT prolongers should be cautious. Patient selection, thorough monitoring, & electrolyte control can reduce these hazards & make ribociclib safer for HR+/HER2- breast cancer therapy <sup>(24)</sup>. The ECG alterations caused by Ribociclib (11.9%) were QT prolongation & T-wave inversion, whereas the cardiac enzymes & EF were normal.

## Conclusion

Ribociclib, abemaciclib, & palbociclib have been shown to slow disease progression & improve patient outcomes in hormone receptor-positive (HR+) & HER2-negative advanced breast cancer patients. All three medications are successful with endocrine therapy, but their toxicity profiles, dosage adjustment needs, & preferred hormonal therapy combinations affect clinical treatment choices.

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