**Original Article**
Middle East Journal of Cancer; April 2025; 16(2): 170-180

# The Effect of Proton Pump Inhibitors on Metastatic Breast Cancer in Patients Treated with CDK4/6i

**Mohamed Khalifa*, MD, Amrallah Mohammed*♦, PhD, Yara Mohamed*, BSc, Isra Mahgoub*, BSc, Mohamed Awadallah*, BSc, Basant SH. Elshafaay**, MD, Amira Hanna**, MD, Ahmed Obaya**, MD, Yaser Arafat*, MD**

**Medical Clinical Oncology Department, Faculty of Medicine, Zagazig University, Egypt*
***Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Zagazig University, Egypt*

Please cite this article as: Khalifa M, Mohammed A, Mohamed Y, Mahgoub I, Awadallah M, Elshafaay BSH, et al. The effect of proton pump inhibitors on metastatic breast cancer in patients treated with CDK4/6i. Middle East J Cancer. 2025;16(2):170-80. doi: 10.30476/mejc.2024.102264.2080.

Received: April 09, 2024; Accepted: August 19, 2024

## Abstract

**Background:** This study aimed to assess the effect of proton pump inhibitors (PPIs) on hormone receptor-positive (HR+) and her-2-negative (her2-) metastatic breast cancer (MBC) in patients receiving CDK4/6i.

**Method:** In a retrospective study, patients were divided into two groups based on their use of PPIs: concomitant use for at least half the treatment period (C-PPIs) and non-concomitant use for less than half the treatment period (NC-PPIs). Statistical analyses were conducted using SPSS 22.0 and MedCalc Software bvba 13.

**Results:** Out of 217 patients, 114 (52.5%) received palbociclib and 103 (47.5%) received ribociclib. Then, 71 palbociclib recipients were combined with aromatase inhibitors (AIs) (43 C-PPIs and 28 NC-PPIs), while 43 were combined with fulvastrant (25 C-PPIs and 18 NC-PPIs). For ribociclib, 82 patients were combined with AIs (71 C-PPIs and 11 NC-PPIs) and 21 were combined with fulvastrant (10 C-PPIs and 11 NC-PPIs). Patients with C-PPI had lower progression-free survival (PFS) than those without C-PPI, palbociclib recipients with AIs or fulvastrant (8.97 months vs. 19.02 months, $P < 0.001$; 13.72 months vs. 18.52 months, $P = 0.04$, respectively) and ribociclib recipients with AIs (10.7 months vs. 19.7 months, $P = 0.05$), but not in patients who received ribociclib with fulvastrant ($P = 0.52$).

**Conclusion:** The simultaneous use of PPIs with palbociclib or ribociclib may be associated with a shorter PFS in HR+, HER2- MBC patients. These results have the potential to enhance clinical decision-making by identifying possible drug interactions and optimizing treatment plans.

***Keywords:*** Proton pump inhibitors, Progression-free survival, Palbociclib, CDK 4/6 inhibitors

♦Corresponding Author:
Amrallah Mohammed, PhD
Medical Clinical Oncology Department, Faculty of Medicine, Zagazig University, Egypt
Tel: 02552604666
Fax: +255125532239
Email: amrallaabdelmoneem@yahoo.com

Copyright: ©Middle East Journal of Cancer. This is an open-access article distributed under the terms of the Creative Commons Attribution-No Derivatives 4.0 International License. This license allows reusers to copy and distribute the material in any medium or format in unadapted form only, and only so long as attribution is given to the creator. The license allows for commercial use.

## Introduction

Metastatic breast cancer (MBC) is considered as a chronic, incurable yet manageable disease because complete response is rare and recurrence is inevitable; thus, patients need to live with their disease in harmony. Accordingly, the primary goal must be to increase survival and improve quality of life while minimizing negative effects.[1]

The hormone receptor-positive (HR+) and her-2-negative (her2-) (HR+/her2-) patient subset comprises approximately 70% of BC patients[2]. Up to half of patients with primary disease will eventually develop metastases, with approximately 6% of patients initially diagnosed with metastatic disease.[3]

Chemotherapy is not the recommended option unless patients have visceral crisis or advanced disease after multiple lines of endocrine treatment.[4]

The benefits of CDK4/6i are consistent across the three CDK4/6i regimens; the three-year OS with hormonal therapy (HT) was 49%, while that with combined HT and CDK4/6i was 73%. The median progression-free survival (PFS) was more than 20 months in the 1st line and 9.5-20.5 months in the 2nd line, with consistent hazard ratios (HRs) across all studies (range: 0.460-0.593).[5]

Up to one-third of all cancer patients are treated with acid reducing agents (ARAs), mostly proton pump inhibitors (PPI), to treat gastritis caused by cancer-related stress and/or cancer-directed therapy.[6,7]

An increase in the availability of ARAs raises the possibility of interactions between oral cancer-directed therapy and pH-dependent solubility.[8]

There is some evidence that concurrent administration of PPIs (C-PPIs) reduces CDK4/6i bioavailability. However, the clinical significance of this interaction is still debated.[9] Therefore, the present retrospective study aimed to evaluate the effect of C-PPIs use of PPIs with CDK4/6i on PFS in patients with HR+/her 2- MBC.

## Patients and Methods

### *Eligibility*

A retrospective medical review study was conducted at the Medical Oncology and Clinical Oncology Departments, Faculty of Medicine, Zagazig University, from January 2019 to December 2022.The study included patients with histopathologically diagnosed HR+/her2- breast cancer, evidence of metastasis, measurable disease, age ≥18 years, and available follow-up data.

### *Ethical aspects*

Before commencing the study, approval was obtained from the Ethics Committee of the Faculty of Medicine at Zagazig University (ethics code: ZU-IRB#231). Since the study was conducted retrospectively with no patient identifiers, the need for informed consent was waived.

### *Immunohistochemistry*

When at least 1% of tumor cells showed positive staining, it was considered indicative of ER and/or PR positivity. Her-2 negative staining was defined as an immunohistochemistry (IHC) score of 0 or 1. If the score is 2, fluorescence in situ hybridization (FISH) results should be negative.

### *Data collection*

Demographic features, disease features, metastatic sites, date/time of CDK4/6i therapy, radiological evaluation, and CA15.3 levels were collected through medical chart review.

### *Patient classifications*

The patients were categorized according to PPIs use into two groups: group A (concomitant use of PPIs; ≥ half the treatment period) and group B (nonconcomitant) use of PPIs; < half the treatment period).

### *Definitions*

Endocrine sensitivity is characterized as patients newly diagnosed with MBC or who experienced a relapse one year or more after completing adjuvant HT. On the other hand, endocrine-resistant patients are those who experienced a relapse while on adjuvant HT, with those relapsing within the first 2 years being classified as primary endocrine-resistant, and those relapsing after 2 years from adjuvant HT being classified as secondary endocrine-resistant. In the case of a metastatic setting, while on HT, progressive disease (PD) within the first 6 months was considered primary endocrine-resistant, and secondary endocrine-resistant PD was considered

**Table 1.** The distribution of clinical features of patients receiving palbociclib treatment with AI across PPI groups

| Features | Total number | PPI | | *P*-value |
|---|---|---|---|---|
| | | NC-PPI | C-PPI | |
| | N = 71 | N = 28 | N = 43 | |
| **Age** | | | | |
| <60 years | 38 | 16 | 22 | 0.62 |
| ≥60 years | 33 | 12 | 21 | |
| **Menopausal status** | | | | |
| Premenopausal | 26 | 11 | 15 | 0.70 |
| Postmenopausal | 45 | 17 | 28 | |
| **Pathology** | | | | |
| IDC | 58 | 24 | 34 | 0.47 |
| Non-IDC | 13 | 4 | 9 | |
| **Hormonal sensitivity** | | | | |
| Sensitive | 70 | 27 | 43 | 0.39 |
| Resistant | 1 | 1 | 0 | |
| **Liver metastasis** | | | | |
| Absent | 47 | 16 | 31 | 0.19 |
| Present | 24 | 12 | 12 | |
| **Lung metastasis** | | | | |
| Absent | 55 | 5 | 30 | 0.54 |
| Present | 162 | 3 | 13 | |
| **Bone metastasis** | | | | |
| Absent | 59 | 26 | 33 | 0.10 |
| Present | 12 | 2 | 10 | |
| **Brain metastasis** | | | | |
| Absent | 69 | 28 | 41 | 0.51 |
| Present | 2 | 0 | 2 | |
| **Lymph node metastasis** | | | | |
| Absent | 57 | 26 | 31 | 0.37 |
| Present | 14 | 2 | 12 | |
| **Dose reduction** | | | | |
| Absent | 57 | 20 | 37 | 0.16 |
| Present | 14 | 8 | 6 | |

AI: Aromatase inhibitors; PPI: Proton pump inhibitor; NC-PPI: Non-concomitant proton pump inhibitor; C-PPI: Concomitant proton pump inhibitor; IDC: Invasive duct carcinoma; $P < 0.05$ is significant.

to be present when the PD ≥ 6 months.[10]

### *Therapy*

The administration of CDK4/6i is based on worldwide recommendations for full-dose or dose modulation, depending on clinical practice and toxicity profiles. Palbociclib was administered once daily at a dose of 125 mg for 21 days followed by 7 days off. Ribociclib was administered at a dose of 600 mg once daily in the morning for 21 days followed by 7 days off (one cycle equals 28 days). Abemaciclib was administered at a dose of 150 mg twice daily.

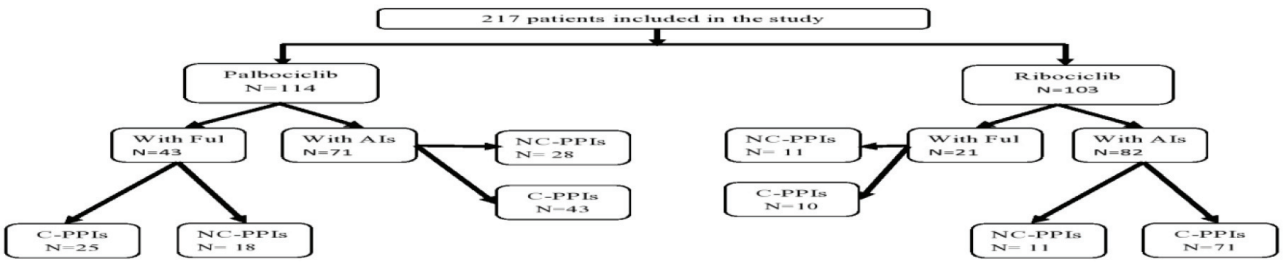
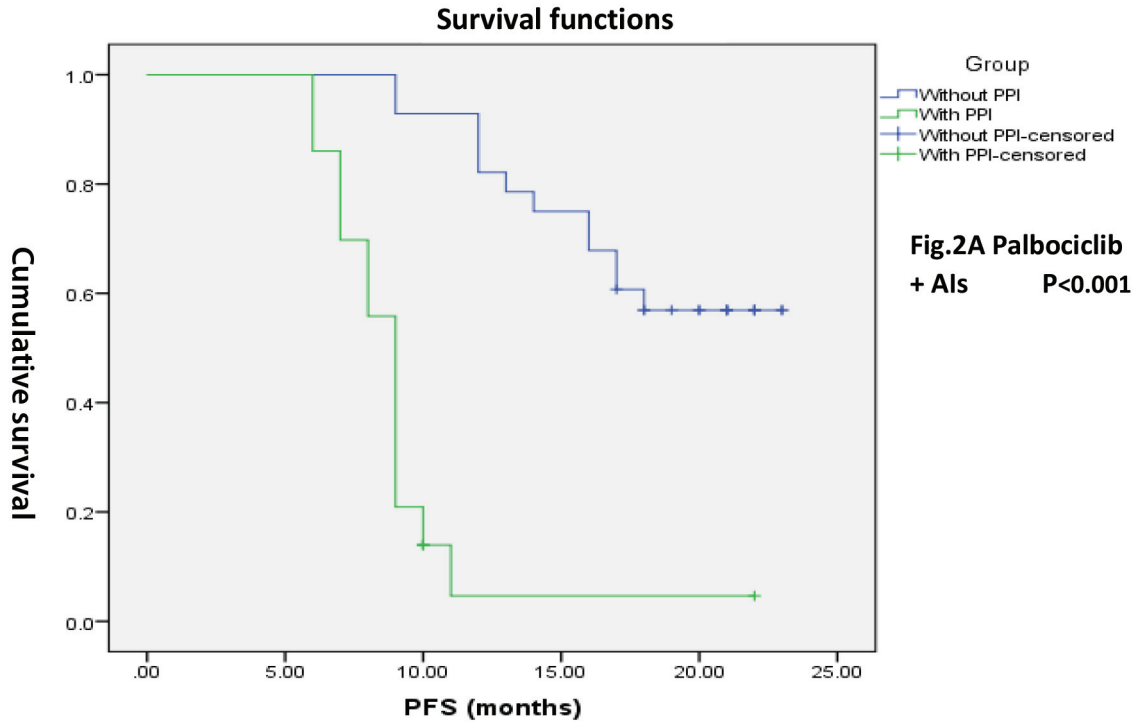



**Figure 1.** This figure displays a study diagram involving 217 patients with mBC HR +ve, Her-2 +ve, clinical and pathological data were available with at least 3 months follow-up.

HR: Hormone receptor; Her-2: Human epidermal growth factor receptor 2; PPIs: Proton pump inhibitors; C-PPIs: Concomitant proton pump inhibitors; NC-PPIs: Non proton pump inhibitors; AIs: Aromatase inhibitors; Ful: Fulvestran



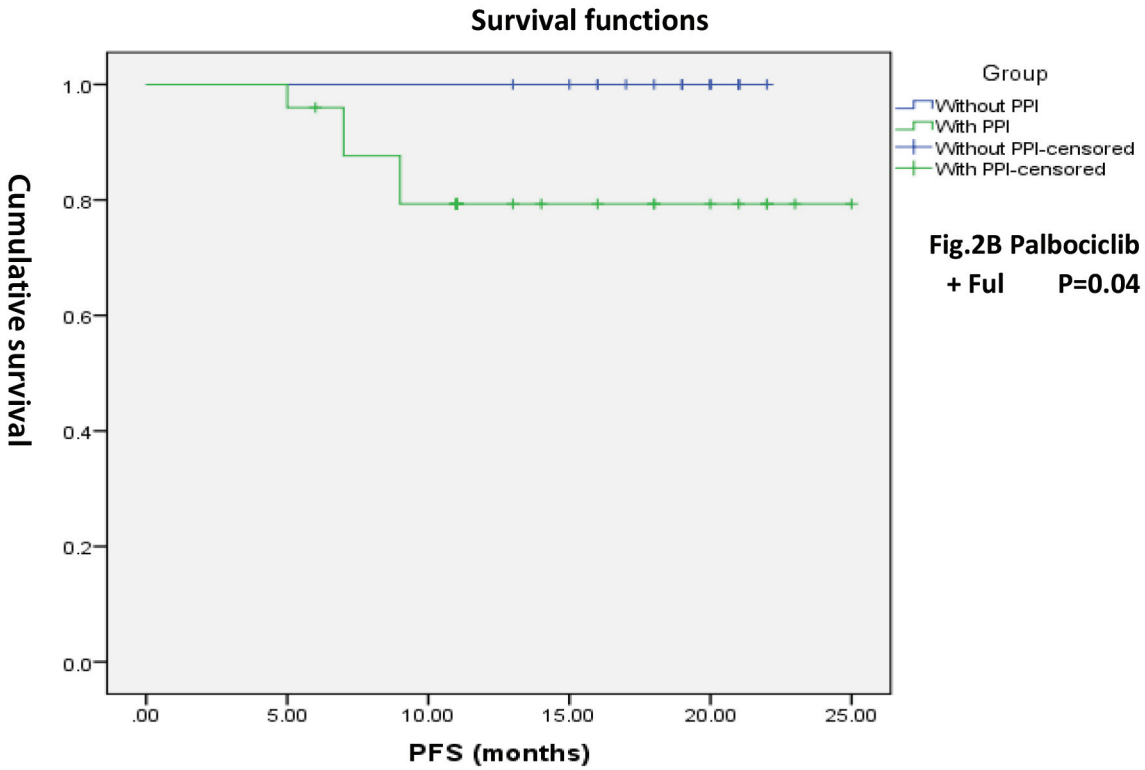




**Figure 2.** A. This figure displays the PFS of patients treated with Palbociclib plus Aromatase inhibitors, showing a significant difference with a *P*-value of <0.001. B. This figure shows the PFS of patients treated with Ful, with a P-value of 0.04.
PFS: Progression-free survival; PPI: Proton pump inhibitors; AIs: Aromatase inhibitors Ful: Fulvestrant

**Table 2.** The distribution of clinical features of patients receiving Palbociclib treatment with Fulvestrant across PPI groups

| Features | Total number N = 43 | PPI | | *P*-value |
|---|---|---|---|---|
| | | NC-PPI N = 18 | C-PPI N = 25 | |
| **Age** | | | | |
| <60 years | 18 | 8 | 10 | 1.000 |
| ≥60 years | 25 | 10 | 15 | |
| **Menopausal status** | | | | |
| Premenopausal | 17 | 7 | 10 | 1.000 |
| Postmenopausal | 26 | 11 | 15 | |
| **Pathology** | | | | |
| IDC | 38 | 14 | 24 | 0.14 |
| Non-IDC | 5 | 4 | 1 | |
| **Hormonal sensitivity** | | | | |
| Sensitive | 37 | 17 | 20 | 0.37 |
| Resistant | 6 | 1 | 5 | |
| **Liver metastasis** | | | | |
| Absent | 33 | 14 | 19 | 1.000 |
| Present | 10 | 4 | 6 | |
| **Lung metastasis** | | | | |
| Absent | 38 | 18 | 20 | 0.62 |
| Present | 5 | 0 | 5 | |
| **Bone metastasis** | | | | |
| Absent | 38 | 18 | 20 | 0.64 |
| Present | 5 | 0 | 5 | |
| **Brain metastasis** | | | | |
| Absent | 40 | 18 | 22 | 0.25 |
| Present | 3 | 0 | 3 | |
| **Lymph node metastasis** | | | | |
| Absent | 39 | 18 | 21 | 0.12 |
| Present | 4 | 0 | 4 | |
| **Dose reduction** | | | | |
| Absent | 35 | 15 | 20 | 1.000 |
| Present | 8 | 3 | 5 | |

PPI: Proton pump inhibitor; NC-PPI: Non-concomitant proton pump inhibitor; C-PPI: Concomitant proton pump inhibitor; IDC: Invasive duct carcinoma. $P< 0.05$ is significant.

The three types of therapy can be combined with one of the following HT: fulvestrant 500 mg once on days 1 and 15 (cycle 1) and then 500 mg once every 28 days ± 3 days (cycle 2 and subsequent) administered as two 250 mg intramuscular injections, letrozole (2.5 mg once daily continuously, orally), or anastrozole (1 mg once daily continuously, oral). In the case of premenopause, we administered 3.6 mg of long-acting goserelin subcutaneously every 4 weeks. The PPIs used were omeprazole (40 mg), lansoprazole (15 mg), and pantoprazole (40 mg) at breakfast.

### *Treatment evaluation*

Every three months, radiological and tumor marker assessments were performed. PFS was compared between the "C- PPIs" and "NC-PPIs" groups.

### *Response Evaluation Criteria in Solid Tumors (RECIST)*

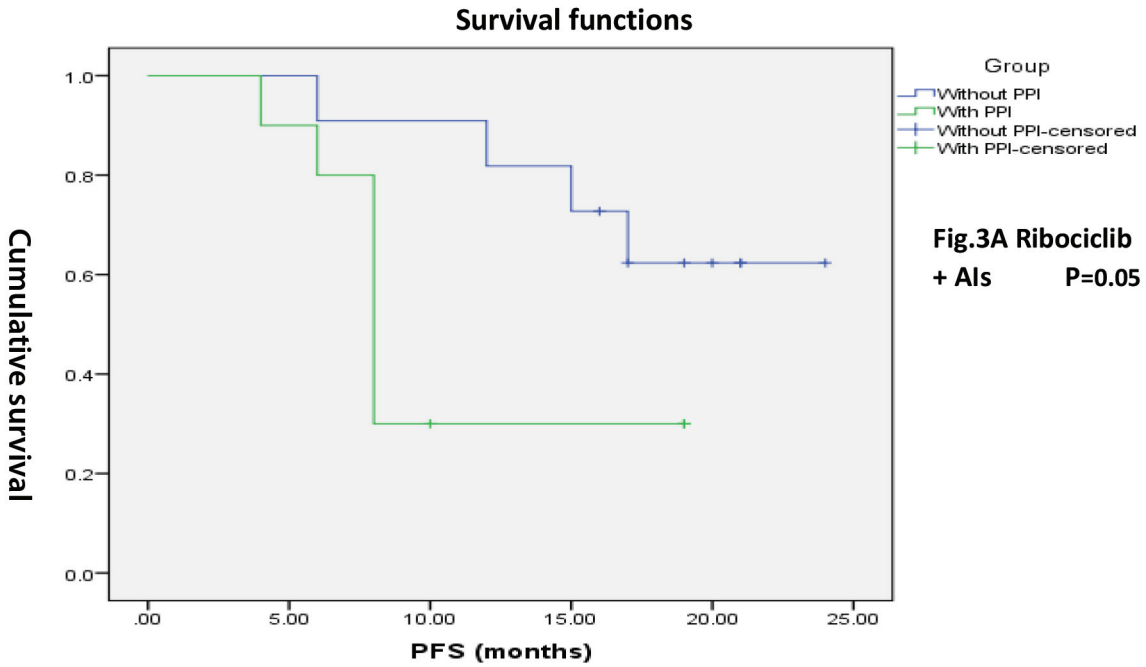
Complete response means all target lesions have disappeared. Partial response (PR) is defined as a minimum 30% decrease in the sum of the long diameter (LD) of target lesions compared with the baseline sum LD. PD is indicated by a minimum 20% increase in the sum of the LD of target lesions compared with the smallest sum LD recorded since treatment initiation or the appearance of new lesions. Stable disease is when there is no significant shrinkage to qualify for PR or increase to qualify for PD, based on the smallest sum LD since treatment initiation.

### *Outcome*

PFS, as the main endpoint, was measured as the time interval between the initiation of CDK4/6i therapy and the occurrence of radiological disease progression or death.

*Statistical analysis*

Continuous variables were expressed as mean ± standard deviation and median (range), and categorical variables were expressed as a number (percentage). Continuous variables were checked for normality using Shapiro-Wilk test. Mann



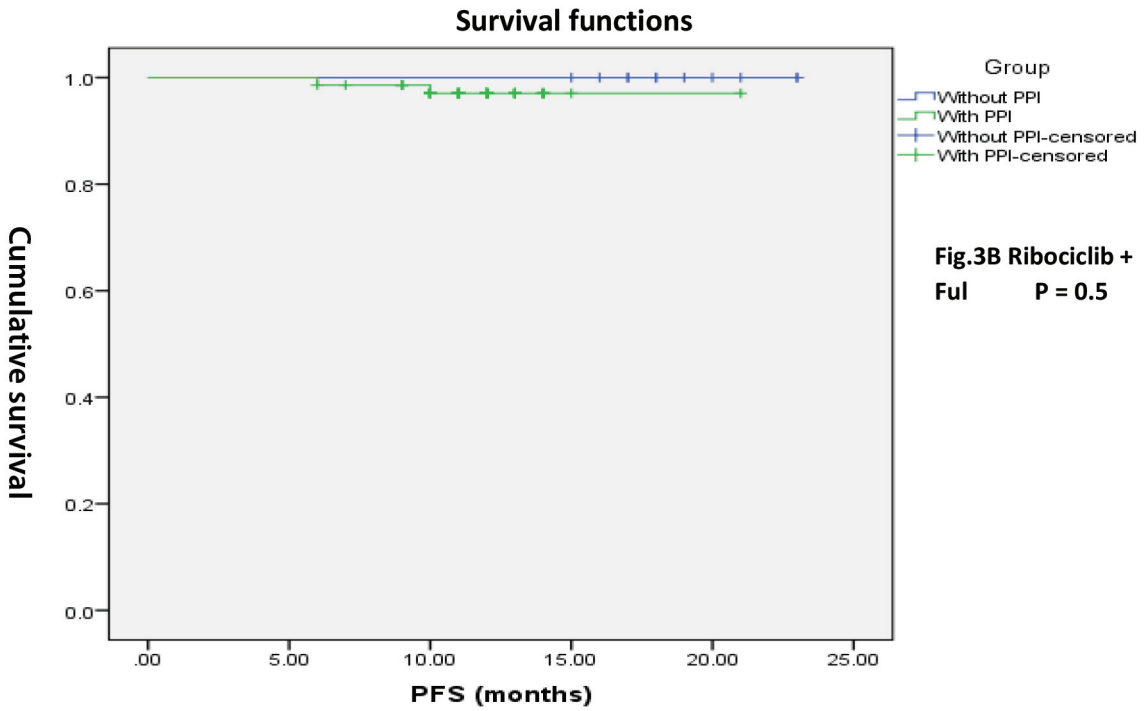




**Figure 3.** A. This figure displays the PFS of patients treated with Ribociclib plus Aromatase inhibitors, showing a statistically significant difference with $P<0.05$. B. This figure shows the PFS of patients treated with Ful, with a $P$-value of 0.5

PFS: Progression-free survival; PPI: Proton pump inhibitors; AIs: Aromatase inhibitors Ful: Fulvestrant

**Table 3.** The distribution of clinical features of patients receiving ribociclib treatment with AI across PPI groups

| Features | Total number N = 82 | PPI | | *P*-value |
|---|---|---|---|---|
| | | NC-PPI N = 11 | C-PPI N = 71 | |
| **Age** | | | | |
| <60 years | 38 | 6 | 32 | 0.55 |
| ≥60 years | 44 | 5 | 39 | |
| **Menopausal status** | | | | |
| Premenopausal | 21 | 4 | 17 | 0.46 |
| Postmenopausal | 61 | 7 | 54 | |
| **Pathology** | | | | |
| IDC | 74 | 11 | 63 | 0.59 |
| Non-IDC | 8 | 0 | 8 | |
| **Hormonal sensitivity** | | | | |
| Sensitive | 79 | 10 | 69 | 0.35 |
| Resistant | 3 | 2 | 1 | |
| **Liver metastasis** | | | | |
| Absent | 53 | 11 | 42 | 0.70 |
| Present | 29 | 0 | 29 | |
| **Lung metastasis** | | | | |
| Absent | 76 | 11 | 65 | 1.000 |
| Present | 6 | 0 | 6 | |
| **Bone metastasis** | | | | |
| Absent | 73 | 11 | 62 | 0.60 |
| Present | 9 | 0 | 9 | |
| **Brain metastasis** | | | | |
| Absent | 81 | 11 | 70 | 1.000 |
| Present | 1 | 0 | 1 | |
| **Lymph node metastasis** | | | | |
| Absent | 74 | 11 | 63 | 0.59 |
| Present | 8 | 0 | 8 | |
| **Dose reduction** | | | | |
| Absent | 67 | 9 | 58 | 1.000 |
| Present | 15 | 2 | 13 | |

AI: Aromatase inhibitors; PPI: Proton pump inhibitor; NC-PPI: Non-concomitant proton pump inhibitor; C-PPI: Concomitant proton pump inhibitor; IDC: Invasive duct carcinoma. $P< 0.05$ is significant

Whitney U test was used to compare two groups of non-normally distributed variables. Percent of categorical variables were compared using Pearson's chi-square test or Fisher's exact test when appropriate. Disease-free survival (DFS) was calculated as the time from date of surgery to relapse or the most recent follow-up in which no relapse was detected. Overall survival (OS) was calculated as the time from diagnosis to death or the most recent follow-up contact (censored). Stratification of DFS and OS was done according to intention to treatment and androgen receptor IHC. These time-to-event distributions were estimated using the method of Kaplan-Meier plot, and compared using two-sided exact log-rank test. Cox regression analysis was used to perform univariate and multivariate models to find independent predictors for DFS and OS. All tests were two sided. All statistics were performed using SPSS 22.0 for windows (IBM Inc., Chicago, IL, USA) and MedCalc windows (MedCalc Software bvba 13, Ostend, Belgium).

## Results

Owing to a lack of data and a small sample size, 14 patients who received abemaciclib (8 combined with AIs and 6 with fulvastrant) were excluded from the analysis. Additionally, the tumor maker; CA15.3 was excluded from the analysis due to inadequate data.

The final analysis included a total of 217 patients, with 114 receiving palbociclib and 103 receiving ribociclib. Among the palbociclib recipients, 71 were combined with AIs (43 C-PPIs and 28 NC-PPIs), while 43 were combined with fulvastrant (25 C-PPIs and 18 NC-PPIs). For ribociclib, 82 patients were combined with AIs (71 C-PPIs and 11 NC-PPIs) and 21 were

**Table 4.** The distribution of clinical features of patients receiving ribociclib treatment with fulvestrant across PPI groups

| Features | Total number N = 21 | PPI | | *P*-value |
|---|---|---|---|---|
| | | NC-PPI N = 11 | C-PPI N = 10 | |
| **Age** | | | | |
| <60 years | 13 | 8 | 5 | 0.38 |
| ≥60 years | 8 | 3 | 5 | |
| **Menopausal status** | | | | |
| Premenopausal | 10 | 5 | 5 | 1.000 |
| Postmenopausal | 11 | 6 | 5 | |
| **Pathology** | | | | |
| IDC | 16 | 8 | 8 | 1.000 |
| Non-IDC | 5 | 3 | 2 | |
| **Hormonal sensitivity** | | | | |
| Sensitive | 21 | 11 | 10 | 1.000 |
| Resistant | 21 | 11 | 10 | |
| **Liver metastasis** | | | | |
| Absent | 13 | 7 | 6 | 0.65 |
| Present | 8 | 5 | 3 | |
| **Lung metastasis** | | | | |
| Absent | 16 | 10 | 6 | 0.14 |
| Present | 5 | 4 | 1 | |
| **Bone metastasis** | | | | |
| Absent | 17 | 10 | 7 | 0.31 |
| Present | 4 | 1 | 3 | |
| **Brain metastasis** | | | | |
| Absent | 21 | 11 | 10 | 1.000 |
| Present | 0 | 0 | 0 | |
| **Lymph node metastasis** | | | | |
| Absent | 20 | 10 | 10 | 1.000 |
| Present | 1 | 1 | 0 | |
| **Dose reduction** | | | | |
| Absent | 18 | 10 | 8 | 0.58 |
| Present | 3 | 1 | 2 | |

PPI: Proton pump inhibitor; NC-PPI: Non-concomitant proton pump inhibitor; C-PPI: Concomitant proton pump inhibitor; IDC: Invasive duct carcinoma. $P < 0.05$ is significant

combined with fulvastrant (10 C-PPIs and 11 NC-PPIs) (Figure 1).

Among patients receiving palbociclib, 71 (62.28%) were on AIs and 43 (37.27%) were on fulvestrant, while in the ribociclib group, 82 (79.61%) were on AIs and 21 (20.38%) were on fulvestrant.

Approximately 6% of patients receiving palbociclib with AI and 3% receiving fulvastrant had their dose reduced, compared with 7% and 1% with ribociclib, respectively.

Totally, 42 patients received omeprazole, 54 received pantoprazole, 46 received esomeprazole, and 10 received lansoprazole. There was no statistically significant correlation found between C-PPIs and NC-PPIs in patients receiving palbociclib and ribociclib (Tables 1-4).

In patients receiving palbociclib with AIs or fulvestrant, those with C-PPI had a lower PFS compared with those without C-PPI (8.97 months vs. 19.02 months, $P < 0.001$; 13.72 months vs. 18.52 months, $P = 0.04$, respectively; Figure 2).

Furthermore, among ribociclib recipients with AIs, patients with C-PPI had a lower PFS than those without C-PPI (10.7 months vs. 19.7 months, $P = 0.05$), but this was not observed in patients who received ribociclib along with fulvastrant ($P = 0.5$; Figure 3).

## Discussion

The present study showed that patients who received palbociclib with AIs or fulvastrant and were C-PPI had a shorter PFS compared with those who were NC-PPI (8.97 months vs. 19.02 months, $P < 0.001$; 13.72 months vs. 18.52 months, $P = 0.04$, respectively).

Our findings were in line with earlier data indicating that the use of palbociclib and NC-

PPIs in treating patients with MBC led to a longer PFS when compared with C-PPIs.[11, 12]

In a retrospective study of 112 patients with MBC treated with palbociclib and HT, Del et al. reported that C-PPI was associated with a shorter PFS and considered an independent predictor of poor survival outcomes.[9]

Additionally, Eser et al. concluded that PPIs decrease stomach pH, leading to a reduction in plasma concentrations of palbociclib. This could potentially impact treatment efficacy and shorten PFS.[13]

These findings support the hypothesis proposed by Goldstein et al., suggesting that long-term use of PPIs may decrease plasma levels of palbociclib below the effective concentration, thereby reducing its efficacy.[14]

On the other hand, these findings contradicted those of Schieber et al., who conducted a chart review of 82 patients with HR+ and her2- MBC who were treated with palbociclib and HT. They concluded that C-PPIs plus palbociclib had no effect on PFS. The differences in outcomes could be attributed to different formulations of the medication used. Previous studies primarily used the capsule form, whereas Schieber et al. administered palbociclib in tablet form. Additionally, there were differences in sample size and patient characteristics.[15]

Furthermore, as compared with NC-PPIs, our study revealed that C-PPIs with ribociclib combined with AIs adversely impacted PFS (10.7 months vs. 19.7 months, $P = 0.05$). But when HT changed to fulvastrant ( $P = 0.52$), the statistical significance disappeared, supporting previous findings.

Chang et al. conducted a systematic review that involved eight trials and included 2584 patients with HR+ and her2- MBC treated with CDK4/6i, either palbociclib or ribociclib, with HT. The patients were categorized into two groups: those with C-PPIs and those not taking. They concluded that although C-PPIs were associated with inferior PFS in patients receiving palbociclib compared with NC-PPIs, ribociclib-receiving patients with C-PPIs were not associated with a detrimental effect on PFS.[16]

Likewise, Çağlayan et al. found no statistically significant difference in PFS among 36 patients treated with ribociclib plus HT.[12]

In a different retrospective study, PFS improved in patients receiving ribociclib with AIs with NC-PPIs as opposed to C-PPIs when combined with fulvastrant ($P = 0.41$).[13]

Samant et al. found through multipronged steps concluded by population pharmacokinetic analysis that a change in stomach pH had no discernible impact on ribociclib bioavailability.[17]

Additionally, Lui et al.'s covariate analysis of the pharmacodynamics and pharmacokinetics of ribociclib revealed that the pharmacokinetics were unaffected by a number of factors, including C-PPIs.[18]

Using a retrospective study including 220 HR+ and her2- MBC MBC patients, 21 of whom received ribociclib, Odabas et al. failed to find a statistically significant association between PFS and C-PPIs with ribociclib combined with AIs, in contrast to our findings.[19]

One of the key factors that influence the absorption and, as a result, bioavailability of a given drug is its solubility at gastric pH. As gastric pH increases, the effectiveness of weak base medications decreases. PPIs-induced increases in gastric pH resulted in a decrease in CDK4/6i plasma levels, which, in turn, shortened PFS.[20]

PPIs assumed to have a negative impact through various mechanisms, but preclinical data do not augment this. Instead, they indicate that PPIs may have antitumor effects against BC cells through inhibiting the proliferation. The shorter PFS of patients using PPIs could be due to factors such as burden of the tumor and the use of non-registered medications.[21] Numerous studies have found that PPIs can interact with oral anticancer therapy, such as tyrosine kinase inhibitors, leading to poor survival outcomes and an increased risk of death. A meta-analysis of 372,418 patients supported these findings.[22-27]

Given the statistically significant correlation between the use of C-PPIs and a poor prognosis in many trials, as measured by a shortened PFS, it is crucial to emphasize the importance of PPIs interaction with CDK4/6i.

Many more interactions may exist that are not

yet known, in addition to those examined in this study. Maximizing the survival outcome should center on avoiding harmful effects caused by common, easily preventable drug interactions.

The lack of evaluation of pharmacokinetic changes of CDK4/6i caused by PPIs is a significant limitation. The retrospective studies rely on individual documentation and are vulnerable to data bias. Additionally, the small sample size and lack of OS analysis and variant analysis are important limitations. Furthermore, we were unable to verify whether the patients actually took the medication and ensure consistent use of PPIs among all patients. Adverse effects were only reported in terms of dose reduction and were underestimated. In this study, palbociclib was in capsule form, so it is unclear if the same results would apply to the tablet form. Further research may be needed to confirm these findings.

## Conclusion

The simultaneous use of PPIs with CDK4/6i, particularly palbociclib, was a potential predictive factor and linked to a shorter PFS. The data on ribociclib is inconclusive.

Patients receiving CDK4/6i or other anticancer drugs that rely on pH for their effectiveness should refrain from prolonged use of PPIs. Instead of PPIs, H2 blockers may be a suitable option. While increasing the dosage of CDK4/6i could theoretically address the problem, it is not practical due to the potential for off-label effects.

## Acknowledgments

I would like to thank the entire medical oncology team for their assistance.

## Funding

None declared.

## Authors' Contributions

All the authors contributed to the design of the study, analysis of data, drafting and reviewing it, approval for publishing, and were included in all aspects of the work. Questions related to the accuracy or integrity of the work were appropriately investigated and resolved.

## Conflict of Interest

None declared.

## References

1. Elfgen C, Montagna G, Schmid SM, Bierbauer W, Güth U. Metastatic breast cancer as a chronic disease: Evidence-based data on a theoretical concept. *Breast Care (Basel)*. 2020;15(3):281-8. doi: 10.1159/000502636. PMID: 32774223; PMCID: PMC7383269.
2. Howlader N, Altekruse SF, Li CI, Chen VW, Clarke CA, Ries LA, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. *J Natl Cancer Inst.* 2014;106(5):dju055. doi: 10.1093/jnci/dju055. PMID: 24777111; PMCID: PMC4580552.
3. Brufsky AM. Long-term management of patients with hormone receptor-positive metastatic breast cancer: Concepts for sequential and combination endocrine-based therapies. *Cancer Treat Rev.* 2017;59:22-32. doi: 10.1016/j.ctrv.2017.06.004. PMID: 28719836.
4. Matutino A, Joy AA, Brezden-Masley C, Chia S, Verma S. Hormone receptor-positive, HER2-negative metastatic breast cancer: redrawing the lines. *Curr Oncol.* 2018;25(Suppl 1):S131-S141. doi: 10.3747/co.25.4000. PMID: 29910656; PMCID: PMC6001771.
5. Piezzo M, Chiodini P, Riemma M, Cocco S, Caputo R, Cianniello D, et al. Progression-free survival and overall survival of CDK 4/6 inhibitors plus endocrine therapy in metastatic breast cancer: A systematic review and meta-analysis. *Int J Mol Sci.* 2020;21(17):6400. doi: 10.3390/ijms21176400. PMID: 32899139; PMCID: PMC7503849.
6. Smelick GS, Heffron TP, Chu L, Dean B, West DA, Duvall SL, et al Prevalence of acid-reducing agents (ARA) in cancer populations and ARA drug-drug interaction potential for molecular targeted agents in clinical development. *Mol Pharm.* 2013;10(11):4055-62. doi: 10.1021/mp400403s. PMID: 24044612.
7. Numico G, Fusco V, Franco P, Roila F. Proton pump inhibitors in cancer patients: how useful they are? A review of the most common indications for their use. *Crit Rev Oncol Hematol.* 2017;111:144-51. doi: 10.1016/j.critrevonc.2017.01.014. PMID: 28259289.
8. Sledge GW Jr, Toi M, Neven P, Sohn J, Inoue K, Pivot X, et al. Monarch 2: abemaciclib in combination with fulvestrant in women with HR+/HER2- advanced breast cancer who had progressed while receiving endocrine therapy. *J Clin Oncol*. 2017;35(25):2875-84. doi: 10.1200/JCO.2017.73.7585. PMID: 28580882.
9. Del Re M, Omarini C, Diodati L, Palleschi M, Meattini I, Crucitta S, et al. Drug-drug interactions between palbociclib and proton pump inhibitors may significantly affect clinical outcome of metastatic breast cancer patients. *ESMO Open.* 2021;6(5):100231. doi: 10.1016/j.esmoop.2021.100231. PMID: 34509802; PMCID: PMC8441157.

10. Cardoso F, Senkus E, Costa A, Papadopoulos E, Aapro M, André F, et al. 4th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 4) dagger. *Ann Oncol.* 2018;29(8):1634-57. doi: 10.1093/annonc/mdy192. PMID: 30032243; PMCID: PMC7360146.
11. de Moraes FCA, Pereira CRM, Sano VKT, Laia EA, Stecca C, Burbano RMR. Do proton pump inhibitors affect the effectiveness of cyclin-dependent kinase 4/6 inhibitors in advanced HR positive, HER2 negative breast cancer? A meta-analysis. *Front Pharmacol.* 2024;15:1352224. doi: 10.3389/fphar.2024.1352224. PMID: 38769999; PMCID: PMC11102992.
12. Çağlayan D, KoÁak MZ, Geredeli Ç, Tatlı AM, Göksu SS, Eryılmaz MK, et al. The effect of concomitant use of proton pump inhibitors with CDK 4/6 inhibitors on survival in metastatic breast cancer. *Eur J Clin Pharmacol.* 2023;79(2):243-8. doi: 10.1007/s00228-022-03435-7. PMID: 36520173.
13. Eser K, Önder AH, Sezer E, Çil T, İnal A, Öztürk B, et al. Proton pump inhibitors may reduce the efficacy of ribociclib and palbociclib in metastatic breast cancer patients based on an observational study. *BMC Cancer.* 2022;22(1):516. doi: 10.1186/s12885-022-09624-y. PMID: 35525929; PMCID: PMC9078089.
14. Goldstein MJ, Peters M, Weber BL, Davis CB. Optimizing the therapeutic window of targeted drugs in oncology: potency-guided first-in-human studies. *Clin Transl Sci.* 2021;14(2):536-43. doi: 10.1111/cts.12902. PMID: 33048459; PMCID: PMC7993318.
15. Schieber T, Steele S, Collins S, Berger M, Fleming M, McLaughlin E, et al. Effect of concurrent proton pump inhibitors with palbociclib tablets for metastatic breast cancer. *Clin Breast Cancer.* 2023;23(6):658-63. doi: 10.1016/j.clbc.2023.05.009. PMID: 37296062.
16. Lee JE, Kwon SH, Kwon S, Jung HI, Nam JH, Lee EK. Concomitant use of proton pump inhibitors and palbociclib among patients with breast cancer. *JAMA Netw Open.* 2023;6(7):e2324852. doi: 10.1001/jamanetworkopen.2023.24852. PMID: 37477917; PMCID: PMC10362477.
17. Samant TS, Dhuria S, Lu Y, Laisney M, Yang S, Grandeury A, et al. Ribociclib bioavailability is not affected by gastric pH changes or food intake: In silico and clinical evaluations. *Clin Pharmacol Ther.* 2018;104(2):374-83. doi: 10.1002/cpt.940. PMID: 29134635; PMCID: PMC6099197.
18. Lu Y, Yang S, Ho YY, Ji Y. Ribociclib population pharmacokinetics and pharmacokinetic/pharmacodynamic analysis of neutrophils in cancer patients. *J Clin Pharmacol.* 2021;61(8):1054-68. doi: 10.1002/jcph.1856. PMID: 33713359.
19. Odabas H, Dogan A, Ozcelik M, Yildirim S, Ozkerim U, Turan N, et al. Does proton pump inhibitors decrease the efficacy of palbociclib and ribociclib in patients with metastatic breast cancer? *Medicina (Kaunas).* 2023;59(3):557. doi: 10.3390/medicina59030557. PMID: 36984558; PMCID: PMC10052377.
20. Willemsen AE, Lubberman FJ, Tol J, Gerritsen WR, van Herpen CM, van Erp NP. Efect of food and acid-reducing agents on the absorption of oral targeted therapies in solid tumors. *Drug Discov Today.* 2016;21(6):962-76. doi: 10.1016/j.drudis.2016.03.002. PMID: 26995271.
21. Ihraiz WG, Ahram M, Bardaweel SK. Proton pump inhibitors enhance chemosensitivity, promote apoptosis, and suppress migration of breast cancer cells. *Acta Pharm.* 2020;70(2):179-90. doi: 10.2478/acph-2020-0020. PMID: 31955147.
22. Fang YH, Yang YH, Hsieh MJ, Hung MS, Lin YC. Concurrent proton-pump inhibitors increase risk of death for lung cancer patients receiving 1st-line geftinib treatment-a nation - wide population-based study. *Cancer Manag Res.* 2019;11:8539-46. doi: 10.2147/CMAR.S222278. PMID: 31572008; PMCID: PMC6756852.
23. Ha VH, Ngo M, Chu MP, Ghosh S, Sawyer MB, Chambers CR. Does gastric acid suppression afectsunitinib efficacy in patients with advanced or metastatic renal cell cancer? *J Oncol Pharm Pract.* 2015;21(3):194-200. doi: 10.1177/1078155214527145. PMID: 24664477.
24. Lalani AA, McKay RR, Lin X, Simantov R, Kaymakcalan MD, Choueiri TK. Proton pump inhibitors and survival outcomes in patients with metastatic renal cell carcinoma. *Clin Genitourin Cancer.* 2017;15(6):724-32. doi: 10.1016/j.clgc.2017.05.019. PMID: 28645482.
25. McAlister RK, Aston J, Pollack M, Du L, Koyama T, Chism D. Effect of concomitant pH-elevating medications with pazopanib on progression-free survival and overall survival in patients with metastatic renal cell carcinoma. *Oncologist.* 2018;23(6):686-92. doi: 10.1634/theoncologist.2017-0578. PMID: 29487220; PMCID: PMC6067930.
26. Veerman GDM, Hussaarts KGAM, Peric R, Oomen-de Hoop E, Landa KD, van der Leest CH, et al. Influence of cow's milk and esomeprazole on the absorption of Erlotinib: A randomized, crossover pharmacokinetic study in lung cancer patients. *Clin Pharmacokinet.* 2021;60(1):69-77. doi: 10.1007/s40262-020-00910-1. PMID: 32557346; PMCID: PMC7808986.
27. Indini A, Petrelli F, Tomasello G, Rijavec E, Facciorusso A, Grossi F, et al. Impact of Use of gastric-acid suppressants and oral anti-cancer agents on survival outcomes: A systematic review and meta-analysis. *Cancers (Basel).* 2020;12(4):998. doi: 10.3390/cancers12040998. PMID: 32325628; PMCID: PMC7226385.