Research Square

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The Effect of Early Neutropenia on PFS with Ribociclib Treatment in Advanced Breast Cancer

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Research Article

Keywords: Breast cancer, CDK 4/6 inhibitors, cerbB2, neutropenia, ribociclib

Posted Date: August 10th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10271772/v1

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Additional Declarations: No competing interests reported.

Abstract

Background

The use of Cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors in the treatment of hormone-positive metastatic breast cancer has led to an increase in disease-free survival. Neutropenia is the most common side effect of this group of drugs and its occurrence at different times in each patient may have prognostic significance.

Materials and Methods

The data of metastatic breast cancer patients who admitted between January 2020 and December 2023 were retrospectively reviewed. 67 patients were included in the study. Among the patients who used ribociclib in addition to endocrine therapy in the first or second series, female patients were included in the study who did not have any biochemical side effects other than neutropenia. The times were determined when neutropenia occurred.

Results

The mean age at diagnosis of 67 female patients was 53.22 ± 11.02 years. Twenty-eight of the patients had metastases in a single site and 39 had metastases in two or more sites. Progression-free survival (PFS) was longer in patients with single-site metastases. PFS was shorter in patients who developed neutropenia in the first 3 months (χ^2=13,769; sd = 2; p = 0,001). Patients who developed neutropenia below 1000 during ribociclib use were found to have a shorter PFS. (χ^2=12,932; sd = 2; p = 0,002). When the estrogen receptor level, progesterone receptor level, Ki67 and PFS levels were compared, no statistically significant difference was found (p > 0.05). PFS was longer in patients with cerbB2 score 1 + than in those with score 2+ (p = 0.005). No effect of NLR (neutrophil/lymphocyte ratio) measured before treatment on PFS was detected.

Conclusion

Neutropenia occurring during the use of ribociclib, a CDK 4/6 inhibitor, affects the duration of advanced breast cancer treatment and the occurrence of neutropenia may be a prognostic indicator. Survival analyses have shown significant associations between neutropenia severity and timing and PFS.

INTRODUCTION

Breast cancer is the most frequently diagnosed cancer in women worldwide [1]. Based on hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2, cerbB2) status, patients are

typically categorized into four molecular subtypes: HR-positive/HER2-negative (HR+/HER2-), HR+/HER2+, HR-/HER2+, and triple-negative breast cancer (TNBC) [2].

Approximately 60–70% of newly diagnosed advanced breast cancer patients are hormone receptor positive [3, 4]. The resistance to endocrine therapy is the most important factor limiting treatment in HR positive patients. Previous research has identified several mechanisms underlying this resistance, including ER loss or mutation, cell cycle signaling molecule rearrangements, ER pathway alterations, and the activation of various escape pathways [5, 6]. Consequently, the emergence of endocrine resistance has necessitated the search for novel therapeutic agents.

CDK4/6 plays a pivotal role in cell cycle regulation and, consequently, in tumor progression [7]. Furthermore, CDK4 has been identified as a key driver of resistance to endocrine therapy [8, 9]. Currently, three CDK4/6 inhibitors—ribociclib, palbociclib, and abemaciclib—are utilized in the metastatic setting. Clinical studies have demonstrated that the co-administration of these inhibitors with endocrine therapy significantly improves overall survival (OS) [10, 11].

The increasing clinical use of this drug class underscores the importance of side-effect management, as maintaining long-term treatment adherence and accuracy is essential for therapeutic success. Interestingly, certain adverse events may serve as indirect biomarkers for treatment efficacy. For instance, studies have shown that the development of an acneiform skin rash in patients receiving EGFR inhibitors correlates with an improved treatment response [12, 13]. Consequently, we aimed to investigate whether neutropenia induced by CDK4/6 inhibitors is similarly associated with clinical outcomes. Specifically, this study evaluates the impact of early-onset neutropenia on progression-free survival (PFS)

MATERIALS AND METHODS

The files of patients were scanned who admitted to the Medical Oncology Clinic of Ondokuz Mayıs University Faculty of Medicine between January 2020 and December 2023. Female patients over the age of 18 who were diagnosed with metastatic breast cancer were included in the study. Patients were included in the study who had previously received any endocrine treatment in the metastatic stage and those who received ribociclib together with endocrine treatment, regardless of the treatment stage. Patients who were given ribociclib orally, 600 mg/day on a 3-week-on, 1-week-off schedule together with letrozole 2.5 mg/day or faslodex 500 mg/month were included in the study. Male patients, patients who continued treatment with ribociclib drug doses below 600 mg, patients with elevated creatinine and ALT and/or AST values requiring drug dose adjustment were excluded from the study.

This study is a retrospective study conducted after written consent was obtained from the Ondokuz Mayis University Faculty of Medicine Clinical Research Ethics Committee. The study was conducted in accordance with the Declaration of Helsinki. Informed consent form was obtained from the patients included in the study.

Statistical Analysis

Statistical analysis of the data obtained from the participants in our study was performed using the IBM Statistics Package for Social Sciences (SPSS version 26.0) program. Continuous variables were expressed using mean±standard deviation, median and minimum-maximum values (minimum-maximum), while categorical variables were expressed using numbers and percentages (%). The suitability of the variables for parametric conditions was evaluated using the Shapiro-Wilk Test.

The Mann-Whitney U Test was used in the analysis of variables between two independent groups that were determined not to meet the parametric conditions and the Kruskal-Wallis Test was used in the analysis of variables between more than two independent groups. When a statistically significant difference was found between variables in more than two independent groups, the groups were compared pairwise using the Mann-Whitney U Test to determine which group caused the difference and Bonferroni correction was applied for the level of significance. Kaplan-Meier method was used for survival analysis with the log-rank test used to statistical difference. A univariate Cox proportional hazards regression model was used to evaluate the prognostic value of each variable for OS. Multivariate Cox proportional hazards regression models were used to analyze independent prognostic factors. The level of statistical significance was accepted as $p < 0.05$.

RESULTS

In our study, the data of a total of 67 metastatic breast cancer women were examined. The demographic characteristics of the patients are given in Table 1. There were 58 patients with ER levels of 50% and above. There were 30 patients with PR levels of 0–49%. There were 34 patients with Ki-67 levels of 20% and above. Among these patients, there were also patients with more than one metastatic site. In particular, 48 patients had bone metastases and 37 patients had lung metastases. In addition, there were 32 patients with metastases in other organs such as the liver and brain. Twenty-eight patients had single-site metastases and 39 had two or more sites (Table 1). PFS was 20.37 months (95% CI, 15.82 to 24.92) in patients with single-site metastases, while it was 13.59 months (95% CI, 10.33 to 16.36) in those with multiple-site metastases. The mean age at diagnosis of female patients with metastatic breast cancer was 53.22 ± 11.02 years. Thirty-seven patients were receiving ribociclib as first-line treatment. The other patients had previously received treatment at the metastatic stage.

Table 1
Demographic characteristics of patients (n = 67)

Demographic characteristics	n (%)
ER Status	4 (5,9)
0–49 (%)	58 (86,6)
50–100 (%)	5 (7,5)
Unknown (%)	
PR Status	30 (44,78)
0–49 (%)	31 (46,26)
50–100 (%)	6 (8,96)
Unknown (%)	
CerbB2 Status	33 (53,6)
Score 0	14 (22,6)
Score 1	15 (24,2)
Score 2	0
Unknown	
Metastasis Sites	28 (41,8)
1 site	28 (41,8)
2 sites	11 (16,4)
3 sites	
Ki67 (%)	14 (20,89)
0–19	34 (50,75)
20 and above	19 (28,36)
Unknown	
Time to Develop Neutropenia	34 (50,75)
(in the first 3 months)	33 (49,25)
1000 and below	
Above 1000	
Endocrine Therapy	31(46,26)
Fulvestrant	33(49,25)

Demographic characteristics	n (%)
Letrozole	1 (1,49)
Anastrazole	2 (2,98)
Unknown	

Table 2
Correlation of immunohistochemical features with PFS

Immunohistochemical Features	n	p
cerbB2	61	**p = 0,021**
score 0–1(+)	47	p = 0,088
score 0–2(+)	48	p = 0,185
score 1(+)-2(+)	29	**p = 0,005**
ER	62	
0–49 (%)	4	p = 0,065
50–100 (%)	58	
PR	61	
0–49 (%)	30	p = 0,065
50–100 (%)	31	
Ki67	48	
0–19 (%)	14	p = 0,547
20 and above	34	

Of the sixty-seven patients included in the study, 6.7% (1/15) had neutrophils above 1000, 36.7% (11/30) had neutrophils below 1000, and 27.3% (6/22) had no neutrophil decrease. Median PFS estimates were calculated as 21.672 months (sd = 2.603; 95% CI: 16.570–26.773) in the neutrophil > 1000 group, 26.506 months (sd = 3.569; 95% CI: 19.511–33.502) in the neutrophil ≤ 1000 group, and 13.642 months (sd = 1.966; 95% CI: 9.790–17.495) in the non-neutropenia group (Fig. 1). The log-rank (Mantel–Cox) test showed that PFS curves differed significantly between groups (χ^2=12.932; sd = 2; p = 0.002).

Analysis of the time to neutropenia revealed that the mean PFS was 21.466 months (sd = 3.541; 95% CI: 14.526–28.406) in the group developing neutropenia before the first 3 months, 27.671 months (sd = 3.020; 95% CI: 21.752–33.590) in the group developing neutropenia after the first 3 months, and 13.901 months (sd = 1.954; 95% CI: 10.071–17.730) in the group that did not develop neutropenia (Fig. 2). The log-rank test showed strong differentiation between groups (χ^2=13.769; sd = 2; p = 0.001).

The median PFS was found to be 22,001 months with fulvestrant (sd = 2.992; 95% CI: 16.137–27.865) and 21,217 months with letrozol (sd = 2.482; 95% CI: 16.353–26.081). The median PFS was 20,000 months with fulvestrant (95% CI: 14.584–25.416) and 20,000 months with letrozol (95% CI: 15.809–24.191), and the fact that the medians of the two main groups were exactly the same indicates that no clinically or statistically significant differences were expected (Fig. 3). The log-rank test is not significant (χ^2=0.778; sd = 2; p = 0.678).

The median PFS was calculated as 19.945 months for cerbB2 score 0 (sd = 2.097; 95% CI: 15.835–24.055), 28.423 months for cerbB2 score 1+ (sd = 5.007; 95% CI: 18.610–38.236), and 17.009 months for cerbB2 score 2+ (sd = 3.192; 95% CI: 10.753–23.265) (Fig. 4). Statistically significant difference was found when cerbB2 score groups were compared with PFS level (p = 0.021). The statistical difference between the groups was due to the difference between score 1(+) and score 2(+) groups and PFS was statistically significant in those with cerb-B2 score 1 + and cerb-B2 score 2+ (p = 0.005) (Table 2).

When other variables, ER level, PR level, Ki67 level and PFS level, were compared, no statistically significant difference was found (Table 2). (p > 0.05). When evaluated in terms of NLR, no significant difference was found in terms of PFS (p = 0.708).

The univariate Cox model established for neutropenia levels below 1000 is statistically significant (Omnibus/Score χ^2=3.943, sd = 1, p = 0.047). The coefficient of the variable is positive (B = 0.446), and the Wald test was found to be significant (Wald = 3.891; p = 0.049). Accordingly, a 1-unit increase in neutropenia level 1000 is associated with a 1.562-fold increase in progression hazard (HR = 1.562).

Univariate Cox analysis for time to neutropenia showed borderline model fit (Omnibus/Score χ^2=3.671, sd = 1, p = 0.055). Although the coefficient of the variable was positive (B = 0.409) and the hazard ratio was HR = 1.505, the Wald test was just above the conventional significance threshold (Wald = 3.612; p = 0.057).

The univariate Cox model is not significant for the cerbB2 variable (Omnibus/Score χ^2=0.088, sd = 1, p = 0.767). The coefficient B = 0.056, hazard ratio HR = 1.057, and Wald test are not significant (Wald = 0.087; p = 0.767).

In univariate Cox regression analysis, variables representing neutropenia status were found to have significant associations with PFS. The model established for neutropenia variables below 1000 was found to be statistically significant (χ^2=3.943; p = 0.047), and each category increase in this variable was associated with a significant increase in progression hazard (HR = 1.562; p = 0.049).

An increased trend towards progression risk was observed for the neutropenia time variable, representing the time to neutropenia development (HR = 1.505), but this association remained at the limit of statistical significance (p = 0.057). In contrast, when cerbB2 scores were evaluated (HR = 1.057; p = 0.767), no significant association was found with PFS.

Variables that were found to be statistically significant in Kaplan–Meier analyses and considered clinically relevant (neutropenia below 1000, time to neutropenia, and cerbB2 scores) were categorically included in the multivariate Cox regression model. The overall fit of the established model was found to be statistically significant (χ^2=20.803; p = 0.004).

In multivariate analysis, neutropenia below 1000 (overall effect p = 0.459) and time to neutropenia (overall effect p = 0.649) did not show statistically significant independent predictors of progression risk. In contrast, significant differences were observed at the category level for the cerbB2 variable. Specifically, patients with a cerbB2 score of 1 + had a significantly lower risk of progression compared to the reference group (HR = 0.070; p = 0.021). Similar, but statistically borderline, effects were observed for other cerbB2 levels.

DISCUSSION

In patients with hormone receptor-positive (HR+) metastatic breast cancer, the prolonged use of endocrine monotherapy frequently leads to the development of endocrine resistance. In this population, the addition of CDK4/6 inhibitors—specifically ribociclib, palbociclib, and abemaciclib—to endocrine therapy has been shown to significantly extend long-term progression-free survival (PFS). While no head-to-head clinical trials currently compare these three inhibitors, treatment selection is typically guided by the clinician’s experience, the drug's toxicity profile, and medication availability.

Since metastatic disease is generally considered incurable, the primary therapeutic goal is to delay disease progression. This study included patients treated with ribociclib in combination with either letrozole or fulvestrant (Faslodex) as endocrine therapy. As there are currently no robust trials directly comparing different endocrine backbones used alongside CDK4/6 inhibitors, such a comparison was beyond the scope of this study.

The heterogeneity of treatment response among patients has led to an extensive search for predictive markers that identify which subgroups derive the greatest benefit. Consequently, prognostic indicators based on routine biochemical parameters—which are cost-effective and easily accessible in daily clinical practice—have emerged as a significant area of interest. It is well established that demographic factors such as age, weight, gender, and race remain unaffected by treatment [14]. In this study, we investigated treatment-induced changes in neutrophil levels and the subsequent time to the onset of neutropenia. Additionally, we evaluated the baseline neutrophil-to-lymphocyte ratio (NLR), immunohistochemically determined ER/PR expression levels, and Cerb-B2 (HER2) scores as potential prognostic criteria.

In our study, no significant relationship was found between ER and PR levels and PFS. Thus, we determined that while a better response to treatment is expected when the ER level is above 50%, treatment response can also be obtained at low ER and PR levels. The NLR cut-off value was examined in the studies by taking it between 2–3, in our study we accepted the NLR cut-off value as 3 and it had no statistically significant relationship with PFS [15, 16].

The majority of newly diagnosed patients are hormone positive and the majority of these patients are cerbB2 negative [17, 18]. CerbB2 negativity is used for score 0, score 1(+) and score 2(+) patients who have been shown not to have amplification with FISH. In our study, we evaluated the relationship between cerbB2 score groups and PFS in patients using ribociclib and found that there was a difference in terms of PFS between score 2(+) and score 1(+) patients. The PFS periods of patients with cerbB2 score 1(+) were longer. In studies, cerbB2 has been held responsible for endocrine resistance [19, 20]. This situation can be explained by increased amplification and decreased response due to endocrine resistance in patients with cerbB2 score 3(+).

Neutropenia is the most common side effect of CDK4/6 inhibitors (for palbociclib and ribociclib). Grade 3 neutropenia can be seen between 12–854 days and it has been determined that it is seen more frequently in the first cycle [21–23].

Kaplan–Meier survival analyses have shown significant associations between neutropenia severity and timing and PFS. These findings suggest that neutropenia developing earlier or more severely may be a clinical indicator that increases the risk of progression. Univariate Cox analyses also showed that neutrophil counts below 1000 were associated with a significant increase in the risk of progression. These results revealed that these variables, representing the severity of neutropenia, have statistically significant effects on PFS, and that this effect is not limited solely to visual survival dissociation.

Univariate Cox analysis for time to neutropenia development showed a trend toward an increased risk of progression, but this association remained at the borderline of statistical significance. This suggests that the timing of neutropenia may be clinically important, but when considered alone, this effect cannot be statistically confirmed due to sample size and event distribution. In contrast, cerbB2 status was not found to be significant in univariate analyses; when modeled linearly, this variable alone was insufficient to explain PFS. Multivariate analysis showed that neutropenia-related variables (specifically neutropenia below 1000 and neutropenia timing), which were significant at the univariate level, lost their significance as independent predictors. This finding suggests that the effect of neutropenia severity and timing on PFS arises not as a standalone and direct mechanism, but rather within a shared domain with other biological and clinical factors. In other words, neutropenia is not positioned as an independent prognostic factor in this cohort.

Febrile neutropenia is seen in 1–2% and there were no febrile neutropenia in our patients. However, we found that early neutropenia (1000 and below) is associated shorter PFS. Although treatment interruptions could potentially explain this, no long-term interruptions occurred in our study group, and patients requiring permanent discontinuation due to persistent neutropenia were excluded. While some literature suggests that side effects—such as anti-EGFR-induced skin rashes—correlate positively with therapeutic response [12, 13], our findings regarding neutropenia and PFS were contrary to these expectations. This discrepancy may be attributed to several confounding factors, including prior treatments, patient age, or comorbid conditions that could influence the timing and severity of neutropenia. Furthermore, since patients receive standardized doses regardless of body mass index

(BMI), variations in drug distribution and pharmacokinetics might negatively impact outcomes. Perhaps the type of endocrine therapy administered in addition to the CDK 4/6 inhibitor and the distribution of these medications in the body may also affect the treatment response. Studies evaluating neutropenia seen in patients who received different treatment steps with a larger number of patients may shed light on this issue. Perhaps, in multicenter studies with a larger number of cases, endocrine treatments combined in the same treatment steps can be compared.

The findings regarding cerbB2 status constituted the most remarkable and clinically significant results of the study. In multivariate Cox analysis, it was found that the risk of progression was significantly lower in patients with a cerbB2 score of 1 + compared to the reference group. These results suggest that cerbB2 status may be not only a defining but also an independent and clinically significant prognostic factor for PFS.

The limitations of this study are the small number of patients, its retrospective nature and being a single-center study. A standardized dosage and administration regimen for all patients may be a limiting factor in optimizing the efficacy of this drug class. Future multicenter studies incorporating more granular data —such as detailed demographic characteristics, concomitant medication use, socioeconomic status, daily physical activity, and even emotional well-being—could significantly contribute to the personalization of treatment. Integrating these multifaceted variables is essential for transitioning toward a precision medicine approach in the management of these patients.

In conclusion, neutropenia remains the most prevalent adverse event associated with ribociclib therapy. Our study investigated this phenomenon and identified a potential correlation between early-onset neutropenia and progression-free survival (PFS). The study revealed that neutropenia-related parameters are associated with PFS, but this association does not have independent prognostic value in multivariate analyses. In contrast, cerbB2 status, particularly at the 1 + score level, has been shown to significantly reduce the risk of progression and have an independent effect on PFS.

Declarations

Disclosures

Ethics Committee Approval: Ethic committee approval was obtained from Ondokuz Mayıs University Ethics Committee.

Conflict of Interest:

None declared.

Authorship Contributions

Concept – D.I.B.; Design – D.I.B.; Supervision – G.D.; Materials – E.I., R.T.; Data collection &/or processing – E.I., M.A.; Analysis and/or interpretation – D.I.B.; Literature serach – D.I.B.,RT.,M.A.; Writing – D.I.B.; Critical review – G.D.

Author Contribution

Authorship Contributions: Concept – Demet Isik BayraktarDesign – Demet Isik BayraktarSupervision – Guzin DemiragMaterials – Elfag Isgandarov, Recep TurkelData collection &/or processing – Elfag Isgandarov, Murat AlanAnalysis and/or interpretation – Demet Isik BayraktarLiterature serach – Demet Isik Bayraktar, Recep Turkel, Mural AlanWriting – Demet Isik BayraktarCritical review – Guzin Demirag

Data availability statement:

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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Figures

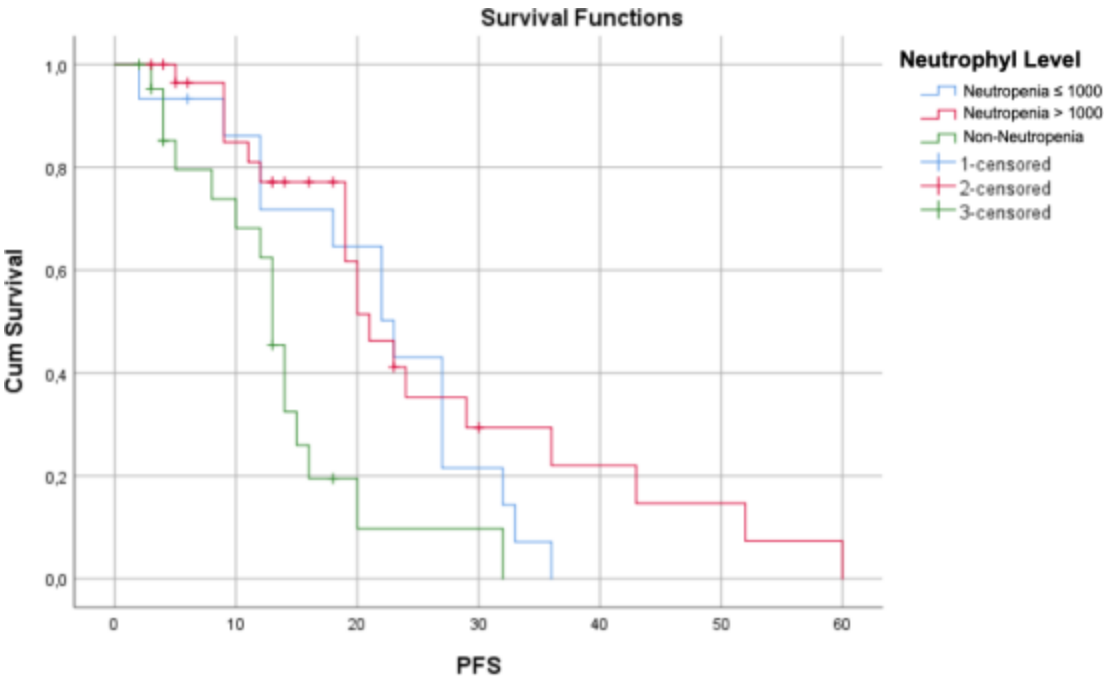


Figure 1

Association of neutrophyl level with PFS.

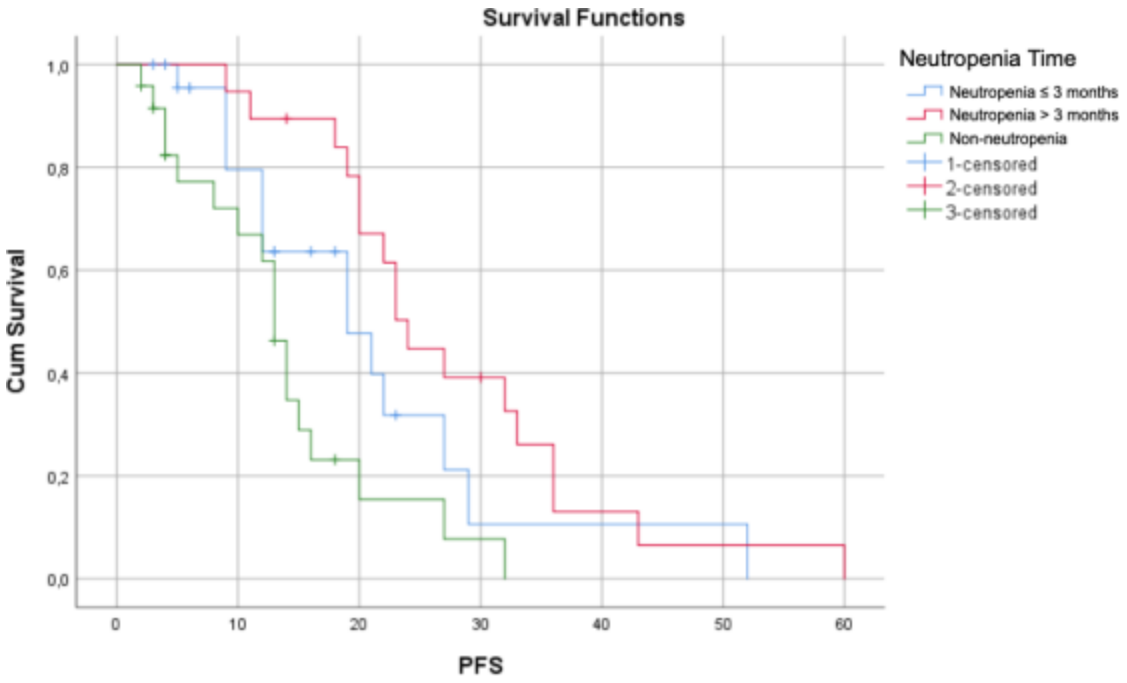


Figure 2

Association of neutropenia time with PFS.

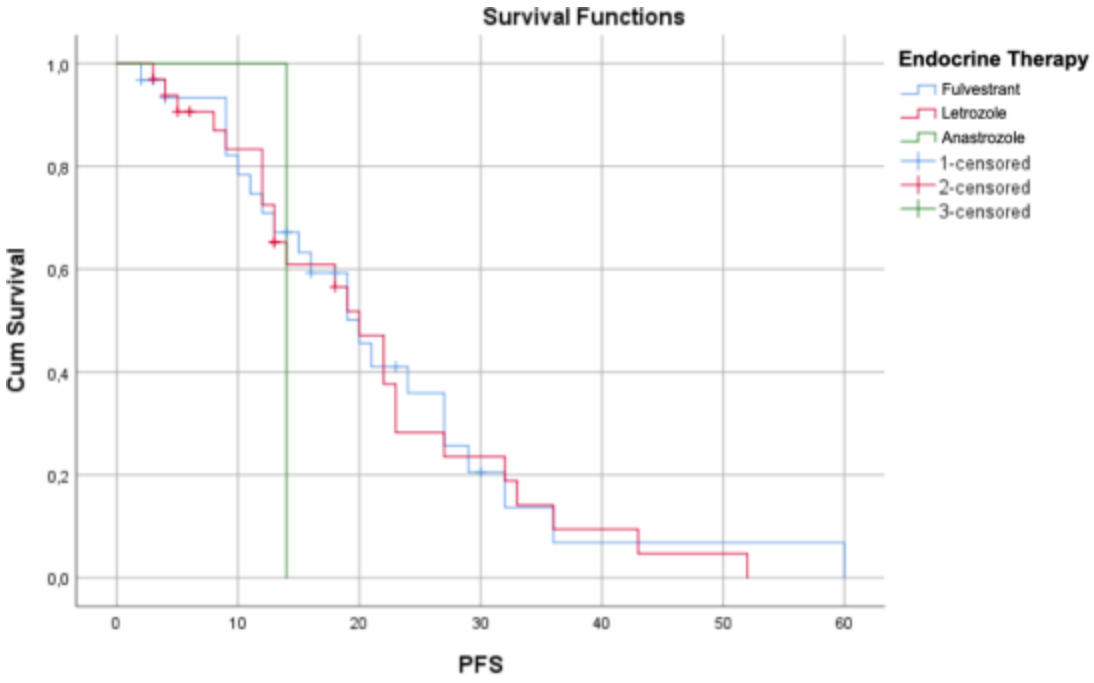


Figure 3

Association of endocrine therapy with PFS.

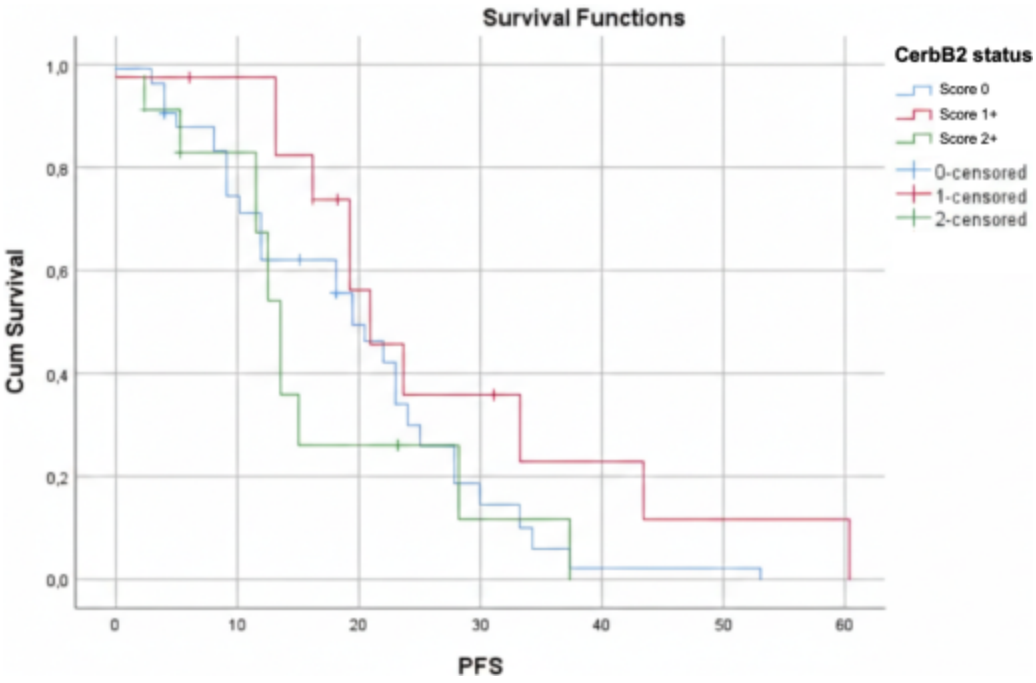


Figure 4

Association of cerbB2 status with PFS.