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Original Article

Clinical Outcomes of Endocrine Therapy Plus CDK4/6 Inhibitors in Elderly Patients with HR+/HER2-Low Metastatic Breast Cancer

Serkan Yaşar[1], Bediz Kurt İnci[1], Pınar Kubilay Tolunay[2], Ergin Aydemir[1], Şura Usta[1], Ali Topkaç[1], Berkan Karabuğa[1], Necla Demir[1], Öztürk Ateş[1], Fatih Yıldız[1]

[1]*University of Health Sciences Türkiye, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Clinic of Medical Oncology, Ankara, Türkiye*
[2]*Ankara University Faculty of Medicine, Department of Medical Oncology, Ankara, Türkiye*

ABSTRACT

Aim: The combination of endocrine therapy (ET) and cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors is the current standard treatment approach for patients with hormone receptor-positive (HR+) / human epidermal growth factor receptor 2-negative (HER2-) metastatic breast cancer (MBC). However, studies specifically evaluating the efficacy of this standard treatment in elderly patients within the HER2-low subgroup, which is considered a new entity, are limited. The aim of our study was to investigate the treatment efficacy and survival data for this specific group.

Methods: Patients with HR+/HER2- MBC defined as HER2-low (+1 or +2 by immunohistochemistry and negative by *in situ* hybridization) who were followed up between 2019 and 2023 were included in the study. The results of 92 patients over the age of 65 who received a CDK4/6 inhibitor and ET for at least 3 months were evaluated.

Results: Our study evaluated 92 patients ≥65 years and older. Survival analyses were conducted for the HER2-low and HER2-zero groups. The median overall survival (OS) for all patients was 108 months [95% confidence interval (CI): 64-152]. In the HER2-low group, the median OS was 88 months (95% CI: 22-154), whereas the median OS was not reached in the HER2-zero group (p=0.054). Although not statistically significant, the difference between the two groups is clearly observed in the Kaplan-Meier graph. Median progression-free survival (PFS) for the overall population was 27 months (95% CI: 15.9-38.1). Similarly, when mPFS was compared between the two groups, outcomes were better in the HER2-zero group, with a median of 34 months (95% CI: 28.8-39.1) versus 17 months (95% CI: 9.2-24.8), which was statistically significant (p=0.026).

Conclusion: The behavior and prognosis of the HER2-low subgroup are still being investigated in recent studies. Our study indicated that the HER2-low group might be associated with poorer survival outcomes and treatment resistance to CDK4/6 inhibitors and endocrine therapy in elderly MBC patients.

Keywords: Cyclin-dependent kinase 4/6 inhibitors, hormone therapy, aged

Introduction

Despite therapeutic advancements, breast cancer remains the most prevalent cancer in women and ranks second in cancer-related mortality [1]. Despite new treatment developments, metastatic breast cancer (MBC) is not yet considered a curable disease. Breast cancer includes different intrinsic subtypes, each with different treatment approaches and prognoses [2,3]. The majority of MBC cases are hormone receptor-positive (HR+), human epidermal growth factor receptor-2-negative (HER2-). The combination of cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors and endocrine therapy (ET) has shown efficacy and safety, and has is proven as standard treatment in first-line and subsequent treatment lines [4,5]. Approximately 20% of all breast cancer cases exhibit HER2 overexpression. Before HER2-targeted therapies, this subtype was associated

Address for Correspondence: Serkan Yaşar MD, University of Health Sciences Türkiye, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Clinic of Medical Oncology, Ankara, Türkiye
E-mail: dr.wetsiz@hotmail.com **ORCID ID:** orcid.org/0000-0002-1465-4131
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with poor prognostic outcomes [6]. Recently, patients exhibiting 1+ and 2+ results via immunohistochemistry (IHC) and testing negative for HER2 using *in situ* hybridization (ISH) were defined as the *HER2-low expression* group.

The HER2-low group represents approximately half of the HER2-non-amplified population. Although the HER2+ group was effectively treated with anti-HER2 monoclonal antibodies for an extended period, the efficacy in the HER2-low group was insufficient [7,8]. Until the results of the latest clinical trials, the prognostic impact of this subgroup was not fully understood, and there was no consensus on the approach to these patients. However, the efficacy of trastuzumab deruxtecan, an antibody-drug conjugate, has been demonstrated in this subgroup, establishing its significance among subsequent-line treatment options [9].

HER2-low breast cancer, similar to HER2+ breast cancer in clinical practice, can be either HR+ or HR-. It may achieve improvements in progression-free survival (PFS) and overall survival (OS) in the metastatic setting through a combination of targeted therapies and hormone therapy [10,11].

Aberrant signaling within growth factor receptor pathways has been recognized as a major contributor to ET resistance in HR+ cancer cells. Clinical and experimental findings indicate that the bidirectional interaction between estrogen receptor and HER2 signaling pathways significantly influences this resistance, potentially leading to treatment failures [12]. Therefore, this situation led researchers to evaluated the treatment efficacies of the HR+/HER2-low group.

Elderly patients are an important population for breast cancer, and considering the increasing incidence of cancer and the different biological behavior of tumors, it is necessary to further investigate the effectiveness of treatment in this subgroup [13].

Age-related changes in pharmacokinetics, pharmacodynamics, and the tumor microenvironment may alter treatment responses and survival outcomes. Which can significantly affect the efficacy and tolerability of cancer treatments [14]. Geriatric patients, particularly those over 65, are frequently underrepresented in clinical trials, leading to a gap in evidence regarding the safety and efficacy of treatments in this group [15]. By focusing on this group, we aim to address this important gap in research and provide insights into how CDK inhibitors may offer tailored treatment strategies, particularly in HER2-low and HER2-zero populations. Several multicenter studies have evaluated the efficacy of CDK4/6 inhibitors and ET for HR+/HER2- MBC in elderly patient groups and have shown that it is generally an effective and tolerable treatment option [16,17]. Another important point is that while there are studies demonstrating the efficacy of CDK 4/6 inhibitors and ET in both the HER2-low and HER2-zero groups, research in the elderly patient population is limited.

The primary aim of the study was to compare the PFS of HER2-low and HER2-zero groups in elderly HR+/HER2- patients receiving CDK4/6 inhibitors and ET. Secondarily, it aimed to evaluate the effects of certain prognostic parameters on PFS, and compare the OS outcomes between the HER2-low and HER2-zero groups.

Methods

Patient Population and Data Collection

The study includes patients aged 65 years and older, with histologically confirmed metastatic HR+/HER2- breast cancer who were monitored between 2019 and 2023, and tolerated treatment with a CDK4/6 inhibitor for at least 3 months.

Patients with a HER2 status of 0 or +1 by IHC or those with a HER2 status of +2 by IHC, but determined to be HER2-negative by ISH, were included in the study. Patients were categorized into two groups: HER2-low (patients with a HER2 status of +1 or +2 by IHC) and HER2-zero (patients with a HER2 status of 0 by IHC). Patients with a second malignancy, those with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) >1, and males were excluded from the study. Systemic treatments and outcomes of 92 eligible patients were recorded.

Ethical approval was obtained from the Non-interventional Clinical Research Ethics Committee of the University of Health Sciences Türkiye, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (decision no: 2025-04/69, date: 17.04.2025). Since the data were collected from medical records without revealing the identities of the participants and the study was retrospective, consent was not obtained from the patients.

Statistical Analysis

Survival outcomes were analyzed using the Kaplan-Meier method, and differences between groups were compared with the log-rank test. Categorical data were presented as counts and proportions (n, %). For continuous variables, depending on the data distribution, either the mean with standard deviation or the median with range was reported. Variables found to be statistically significant ($p \leq 0.05$) in univariate analyses were included in the multivariate regression model to determine the independent determinants of the outcome. A p of <0.05 was accepted as the threshold for statistical significance. We used Statistical Package for the Social Sciences version 25.0 (IBM Corp., Armonk, NY, USA) to perform all statistical analyses.

Results

Of the patients included in the study, 33.7% (n=31) were classified as HER2-low, while 66.3% (n=61) were categorized as HER2-zero. Among the HER2-low group, 21.7% (n=20) had a HER2 status of 1+ by IHC and 12% (n=11) had a HER2 status of 2+ but were determined to be HER2-negative by ISH. The groups were similar in clinical and demographic characteristics, including comorbidity status, visceral and non-visceral metastasis, metachronous and *de novo* metastasis rates, line of therapy, endocrine treatment, and choice of CDK 4/6 inhibitor (Table 1).

The mean age at treatment initiation was 72.9±5.8 years. A total of 68 patients were treated with a CDK4/6 inhibitor and ET in the first line, whereas 24 patients received these treatments in the second line. In the subgroups, 71% (n=22) of the HER2-low group received combination therapy as first-line treatment, while 29% (n=9) received it as second-line treatment. In the HER2-zero group, 75.4% (n=46) were treated with combination therapy in the first line, and 24.6% (n=15) in the second line.

The impact of comorbidities, metastatic status, site of metastasis, type of CDK 4/6 inhibitor, and HER2 status on mPFS was evaluated using univariate analysis. Among these factors, only HER2 status was found to have a significant effect on mPFS (p=0.03).

The median PFS for the overall population was 27 months [95% confidence interval (CI): 15.9-38.1]. When comparing mPFS between the two groups, the HER2-zero group demonstrated better outcomes, with a median of 34 months (95% CI: 28.8-39.1) compared to 17 months (95% CI: 9.2-24.8) in the HER2-low group, a difference that was statistically significant (p=0.026) (Figure 1). Among patients who received CDK4/6 inhibitor and ET in the first line setting, the mPFS was 43 months (95% CI: 31-55) in the HER2-zero group, compared to 24 months (95% CI: 14.7-33.2) in the HER2-low group. This difference was statistically significant (p=0.049).

The median OS for the entire study population was 108 months (95% CI: 64-152). In the HER2-low group, the median OS was 88 months (95% CI: 22-154), whereas it was not reached in the HER2-zero group. Although statistical significance was not achieved, a notable trend was observed (Figure 2). At a median follow-up of 40 months (95% CI: 30-50), mOS was not reached in either of the HER2-low or the HER2-zero groups.

Discussion

Among breast cancer subtypes, HR-positive/HER2-negative disease is the most frequently observed, comprising roughly 66% of MBC diagnoses [18].

As a result of recent studies, the combination of CDK4/6 inhibitors and ET has become the new standard treatment for HR+/HER2- MBC and has been included in guideline recommendations [19].

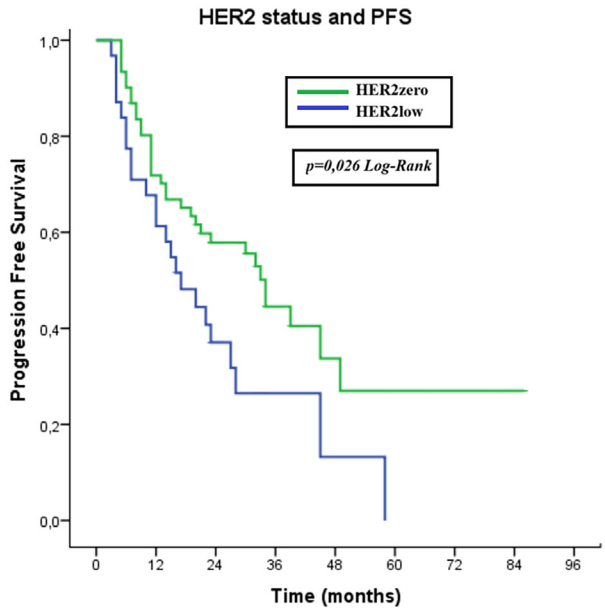

Figure 1. Kaplan-Meier curve for PFS according to HER2-low and HER2-Zero
PFS: Progression-free survival, HER2: Human epidermal growth factor receptor 2-negative

Table 1. Clinical characteristics of the patients

HER2 status	HER2-low n (%)	HER2-zero n (%)	p
Comorbidity Available Not-available	 22 (71) 9 (29)	 46 (75.4) 15 (24.6)	0.646*
Metastatic status Recurrent (secondary resistance) *De novo*	 16 (51.6) 15 (48.4)	 34 (55.7) 27 (44.3)	0.707*
Metastatic sites Non-visceral Visceral	 16 (51.6) 15 (48.4)	 27 (44.3) 34 (55.7)	0.504*
Treatment line 1 2	 22 (71) 9 (29)	 46 (75.4) 15 (24.6)	0.646*
Treatment option Ribociclib Palbociclib	 14 (45.2) 17 (54.8)	 33 (54.1) 28 (45.9)	0.418*
Endocrine therapy AI SERD	 16 (51.6) 15 (48.4)	 38 (62.3) 23 (37.7)	0.325*

*p<0.05
AI: Aromatase inhibitor, SERD: Selective estrogen receptor degrader, HER2: Human epidermal growth factor receptor 2-negative

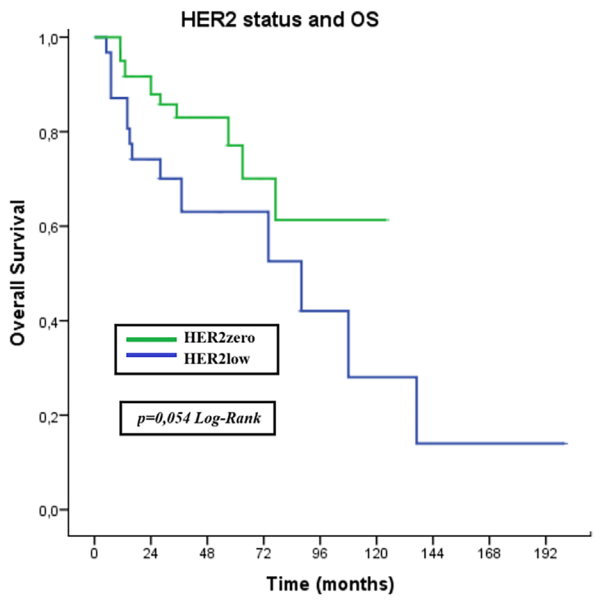

Figure 2. Kaplan Meier curve for OS according to HER2-Low and HER2-Zero
OS: Overall survival, HER2: Human epidermal growth factor receptor 2-negative

HER2-negative disease was historically regarded as a single entity, prior to the recognition and characterization of HER2-low as a distinct subgroup in contemporary research. We know that the differential efficacy of CDK4/6 inhibitors between HER2-low and HER2-zero tumors is not fully established. This study provides compelling evidence supporting the efficacy of CDK4/6 inhibitors in both HER2-low and HER2-zero subgroups, particularly in the elderly population (age 65 years and older), and highlights the importance of addressing the unique characteristics and treatment challenges faced by this underrepresented group in oncology. By limiting our cohort to patients aged 65 years and older, we aimed to reduce heterogeneity and provide more clinically relevant insights for this growing patient group. Although our results focus on treatment efficacy, they are very important as a source of inspiration for translational and clinical research.

Previous studies, such as the study by Schettini et al. [20], have emphasized clinicopathological differences between HER2-low and HER2-zero subtypes, including higher frequency of nodal involvement and larger tumor size in HER2-low tumors. Although our study did not focus on such baseline characteristics, our findings provide additional insight by demonstrating that these biological differences might also translate into differential treatment responses to CDK4/6 inhibitors in the elderly population.

Zattarin et al. [21] found that HER2-low status was associated with significantly worse PFS and OS in patients with HR+/HER2- advanced breast cancer receiving CDK 4/6 inhibitors and ET. Median PFS was 23.6 months in the HER2-low group vs. 32.3 months in the HER2-zero group (p=0.014); OS was 48.7 vs. 58.3 months, respectively (p=0.029). Similar to our study, HER2 status may constitute an independent and significant risk factor for both PFS and OS in this patient group.

In a similarly designed study evaluating 258 metastatic patients, a substantial numerical difference in PFS was observed between the groups (HER2-low and zero), although it did not reach statistical significance. This difference was nearly twofold. mPFS in the HER2-low group was 27.6 months compared with 44.3 months in the HER2-zero group (p=0.341). Furthermore, in patients treated with ribociclib, a more pronounced difference was observed, with the HER2-low group showing a MmPFS of 24.2 months compared to 53.1 months in the HER2-zero group [22]. Two key differences of this study are that it included only patients receiving first-line therapy and that the number of patients treated with ribociclib as the CDK4/6 inhibitor was higher. In our study, when we specifically analyzed the subgroup of patients who received first-line treatment, similar PFS outcomes were observed compared to those reported in a previous study. This finding suggests that, even when focusing on the geriatric patient population, survival outcomes comparable to those reported in the literature can be achieved in older age groups as well.

However, some studies have shown no significant difference. Guliyev et al. [23] reported similar PFS and OS outcomes between HER2-low and HER2-zero groups (mPFS: 25.2 vs. 22.6 months, mOS: NR vs. 37.5 months; p=0.972, p=0.707, respectively). The discrepancy between our study and the current one may be explained by the differing distributions of *de novo* and recurrent metastatic patients, a parameter that inherently includes prognostic factors such as endocrine resistance, which can significantly impact survival outcomes. Similarly, Ralser et al. [24] found no difference in mPFS (17 vs. 18 months) and also observed no significant impact of HER2 status conversion between primary and metastatic tissues.

There are also studies evaluating the efficacy of CDK4/6 inhibitors and ET in elderly patients, which are the patient group assessed in our study. In a study conducted by Pla et al. [16], it was demonstrated that patients in the geriatric age group (>70 years) achieved similar outcomes in terms of PFS and OS compared to younger patient groups, both in first-line and second-line treatment settings. This study demonstrates that it is an effective and safe treatment option for the geriatric population. Although this study includes a similar number of geriatric patients to our own, it does not provide an additional analysis regarding the relationship between HER2-low or HER2-zero status and survival outcomes.

While HER2 status is a potential risk factor, current evidence is conflicting, especially for elderly patients, a population typically underrepresented in clinical trials. Moreover, treatment development in this group progresses more slowly. Studies often evaluate HER2-low and elderly patients separately, and to our knowledge, no prior study has focused specifically on elderly patients with HER2-low disease. Our single-center study addresses this gap and, by including a relatively large elderly cohort with uniform follow-up, offers insights which may assist in guiding future research and treatment approaches.

Study Limitations

The study has several limitations. First, while the single-center design helps eliminate follow-up heterogeneity, it also limits the generalizability of the findings to a broader population. Secondly, to ensure an adequate sample size in our single center cohort, patients receiving first and second line treatments were analyzed together; although the characteristics were similar across HER2 status, this approach may introduce bias. Larger, multicenter studies with sufficient patient numbers and stratified analyses by treatment line are needed to draw more definitive conclusions and strengthen the evidence base. One of our limitations is that more than 50% of the patients used palbociclib. Until recent developments, we believed there was no difference in survival in patients treated with CDK 4/6 inhibitors. Therefore, there are many studies in which palbociclib is used frequently, as in our study. Therefore, this distribution reflects real life rather than treatment selection bias. Another factor was the patients' PS, evaluated using the ECOG performance scale; only patients with ECOG scores of 0-1 were included. In the elderly patient group, incorporating frailty assessments into the evaluation process may contribute to the selection of patient populations with better treatment tolerance, thus improving the relevance and applicability of treatment outcomes.

Conclusion

Our study specifically investigated the efficacy of CDK4/6 inhibitors in the HR+/HER2-low subgroup of elderly patients with MBC, an area that is largely under-researched in the current literature. Despite ongoing debate regarding the prognostic implications of the HER2-low phenotype, our findings suggest that this subgroup may have reduced sensitivity to CDK4/6 inhibitors, with outcomes in the geriatric population similar to those in other age groups. By addressing this knowledge gap, our study not only adds meaningful data to the limited available evidence, but also highlights the need for further research to optimize treatment strategies and improve clinical outcomes in this patient group.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Non-interventional Clinical Research Ethics Committee of the University of Health Sciences Türkiye, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (decision no: 2025-04/69, date: 17.04.2025).

Informed Consent: Since the data were collected from medical records without revealing the identities of the participants and the study was retrospective, consent was not obtained from the patients.

Footnotes

Authorship Contributions

Concept: S.Y., B.K.İ., Design: S.Y., B.K.İ., B.K., F.Y., Data Collection or Processing: P.K.T., E.A., A.T., N.D., Analysis or Interpretation: S.Y.,B.K.İ. Literature Search: Ş.U., Ö.A., Writing: S.Y., F.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

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